INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/07748

	TO STATE OF STATE OF MATTER						
A. CLASSIFICATION OF SUBJECT MATTER							
IPC(8) : C12Q 1/68; C07H 21/04 US CL : 435/6; 536/23.1, 23.5							
According to	International Patent Classification (IPC) or to both nati	onal classification and IPC					
B. FIELD	OS SEARCHED						
Minimum doc	cumentation searched (classification system followed by	y classification symbols)	}				
U.S. : 43	5/6; 536/23.1, 23.5						
D	on searched other than minimum documentation to the	extent that such documents are included in	the fields searched				
Documentation	on searched outer than hammen development						
		Classes and whose practice ble sear	ch terms used)				
Electronic dat	ta base consulted during the international search (name	of data base and, where practicators, some	,				
Please See Co	ontinuation Sheet						
C. DOCT	JMENTS CONSIDERED TO BE RELEVANT	Cal I t page age 6	Relevant to claim No.				
Category *	Citation of document, with indication, where ap	propriate, of the relevant passages	1-4				
Х	US 5,776,683 A (SMITH et al) 07 July 1998 (07.07.1	1998), especially col. 6, 23 and 12 of 7.	• •				
	SQUIRE et al. High-resolution mapping of amplificat	tions and deletions in pediatric	1-4				
Y	osteosarcoma by use of CGH analysis of cDNA micro	parrays. Genes, Chromosomes &					
	Cancer. 2003, Vol. 38, pages 215-225, especially pag	ge 216 and Table 1.	1				
			1				
			į				
		:	1				
		,					
	·						
	r documents are listed in the continuation of Box C.	See patent family annex.					
	Special categories of cited documents:	"T" later document published after the inten	national filing date or priority date				
1		and not in conflict with the application to principle or theory underlying the inven	tion				
	t defining the general state of the art which is not considered to be of r relevance	a state and the of	aimed invention cannot be				
	plication or patent published on or after the international filing date	considered novel or cannot be considered	ed to involve an inventive step				
		when the document is taken salone					
"L" documen	it which may throw doubts on priority claim(s) or which is cited to the publication date of another citation or other special reason (as	"Y" document of particular relevance; the cl considered to involve an inventive step	aimed invention cannot be				
specified		with one or more other such clocuments	, such combination being obvious				
"O" documen	at referring to an oral disclosure, use, exhibition or other means	to a person skilled in the art					
li .	at published prior to the international filing date but later than the	"&" document member of the sarrie patent f	amily				
"P" document	it published prior to the international rating outs out save than a						
Date of the	actual completion of the international search	Date of mailing of the international sear	rch report				
!		ST LER SIM	j				
18 January 2006 (18.01.2006) Authorized offices							
Name and n	nailing address of the ISA/US	Moritale muse	see for				
	ail Stop PCT, Attn: ISA/US commissioner for Patents	Carra Myers	/-/				
P.0	O. Box 1450	Telephone No. 571-272-1600					
Facsimile N	Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201						

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/07748

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)							
This internat	ional search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:						
1.	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:						
2.	Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:						
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).						
Box No. III	Observations where unity of invention is lacking (Continuation of item 3 of first sheet)						
This International Searching Authority found multiple inventions in this international application, as follows: Please See Continuation Sheet							
	\mathscr{A}_{\cdot}						
1.	As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.						
2.	As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.						
3.	As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:						
4.	No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-4, with respect to the amplicon						
	comprising chromosome 8q24.13						
Remark on I							
Remark on I	Protest The additional search fees were accompanied by the applicant's protest and, where applicable, the						

Form PCT/ISA/210 (continuation of first sheet(2)) (April 2005)

INTERNATIONAL SEARCH REPORT P

International application No. PCT/US05/07748

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional examination fees must be paid.

Groups 1-47, claims 1-4 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing one of the 47 amplicons set forth in Table 2. For example, Group 1 is drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing the 5.3 MB amplicon comprising chromosome 8q24.13. Upon election of one of the groups, please specify the amplicon to be searched.

Groups 48-3097, claims 5-9 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing one of the sequences of SEQ ID NO: 1-3049 and assaying for a change in the level of expression of one of the sequences. For example, Group 48 is drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing SEQ ID NO: 1. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

Groups 3098-6147, claims 10-11 (in part), drawn to methods for identifying a cancerous state of a cell by assaying for the sequence of one of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

Groups 6148-9196, claims 12-34 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049 and assaying for a change in the activity of the polypeptide. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched. Further, it is noted that claim 23 has been included with this grouping because it appears that claim 23 intends to depend from claim 15, rather than claim 11.

Groups 9197-12,245, claims 35-39 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing one of the sequences of SEQ ID NO: 1-3049 and assaying for a change in the cancer cell growth of said cell. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

Groups 12,246-15,294, claims 40-47 (in part), drawn to methods for treating cancer by using a compound that effects the activity of a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the corresponding SEQ ID NO of the elected group to be searched.

INTERNATIONAL SEARCH REPORT

International application No. PCT/US05/07748

Groups 15295-18343, claims 48-55 and 57-60 (in part), drawn to methods for monitoring the progress of a cancer therapy by assaying for the level of a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

Groups 18,344-21,392, claim 56 (in part), drawn to methods for producing data comprising producing test data sufficient to identify the chemical nature of a test compound that effects the activity of a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

The inventions listed as Groups 1-21,392 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

In accordance with 37 CFR 1.475(d) Applicant is entitled to an examination of the first product, method of making said product and method of using said product. In the instant case, the first method is one which requires one of the 47 amplicons of Table 2. This product is not required for the methods set forth in the remaining groups. Thereby, Groups 48-21,392 constitute distinct groups which do not share the same corresponding technical feature of groups 1-47. Further, unity of invention exists only when there is a technical relationship among those inventions involving one or more of the same or corresponding technical features. The expression 'special technical feature" means those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. The technical feature linking the claims 5-60 is the HAS2 gene. However, the HAS2 gene was known in the art at the time the invention was and thereby does not constitute a contribution over the prior art (see NCBI Database, GenBank Accession No. U54804). Accordingly, there is no special technical feature linking the recited groups, as would be necessary to fulfill the requirement for unity of invention.

It is also noted that each of the present claims has been presented in improper Markush format, as distinct methods are improperly joined in the claims. Each amplicon of Table 2 and each nucleic acid sequence of SEQ ID NO: 1-3049 is structurally and functionally distinct from and has a different special technical feature than each other the amplicons and nucleic acid sequences. The chemical structure of each amplicon and nucleic acid sequence differ

from each other. For example, a polynucleotide comprising SEQ ID NO: 1 is chemically, structurally, and functionally different from a molecule comprising SEQ ID NO: 2. Given the differences in the structure, function and effect the amplicons of Table 2 and the sequences of SEQ ID NO: 1-3049, these compounds are not considered to share a special technical feature as would be necessary to fulfill the requirement for unity of invention. These distinct compounds do not have both a "common property or activity" and a common structure as would be required to show that the inventions are "of a similar nature." As the products and methods encompassed by the claims do not share a special technical feature, the distinct products and methods may not properly be presented in the alternative. Accordingly, the claims have been separated into a number of groups corresponding to the number of different inventions encompassed by the claims, and the claims will be searched only as they read upon the invention of the elected group

Additionally, each of the claimed methods have different objectives and require different process steps. The methods of claims 1-4 require cells containing one of the amplicons of Table 2 and requires assaying for a change in the amplification ratio of the amplicon. The methods of claims 5-9 require the use cells that contain one of the sequences of SEQ ID NO: 1-3049, and requires assaying for a change in gene expression by assaying for mRNA or protein levels in order to

accomplish the objective of identifying a antineoplastic agent. The methods of claims 10-11 require assaying for the level of one of the sequences of SEQ ID NO: 1-3049 in order to accomplish the objective of identifying a cancerous state of a cell. The methods of claims 12-34

require contacting a cell with a test agent and assaying for a change in biological activity of a polypeptide encoded by SEQ ID NO: 1-3049. The methods of claims 35-39 require contacting a cell with a test compound and assaying for the cancerous state of a cell. The methods of

claims 40-47 require administering an agent to an individual in order to accomplish the objective of treating cancer. The methods of claims 48-55 and 57-60 require determining gene expression levels of a polypeptide of one of SEQ ID NO: 1-3049 and assaying for polypeptide levels in order to accomplish the objective of monitoring the progress of cancer therapy. The method of claim 56 requires identifying test compounds that have

Form PCT/ISA/210 (extra sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No. PCT/US05/07748

antineoplastic activity and producing test data in order to obtain sufficient data to identify the chemical structure of the test compound. In addition to differences in objectives, effects, and method steps, it is again noted that the claims of the present Groups are not directed to the detection or identification of molecules having the same or common special technical feature, for the reasons discussed above.								
Continuation of B. FIELDS SEARCHED Item 3: WEST: USPT, JPAB, EPAB, DWPI, PGPUB; DIALOG: MEDLINE, CA, BIOSIS, EMBASE search terms: 8q24.13, 8q24.1; amplification or amplified or copy number; cancer or tumor or neoplasm								

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date 30 March 2006 (30.03.2006)

(10) International Publication Number WO 2006/033664 A1

(51) International Patent Classification: C12Q 1/68 (2006.01) C07H 21/04 (2006.01)

(21) International Application Number:

PCT/US2005/007748

(22) International Filing Date: 8 March 2005 (08.03.2005)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data: 60/550,304

8 March 2004 (08.03.2004) U

(71) Applicant (for all designated States except US): AVALON PHARMACEUTICALS [US/US]; 20358 Seneca Meadows Parkway, Germantown, MD 20876 (US).

(72) Inventors; and

- (75) Inventors/Applicants (for US only): STROVEL, Jeffrey, W. [US/US]; 14622 Keeneland Circle, North Potomac, MD 20878 (US). CAIN, Colyn, B. [US/US]; 4309 Kentbury Drive, Bethesda, MD 20814 (US). HORRIGAN, Stephen, K. [US/US]; 1895 Millboro Drive, Potomac, MD 20854 (US). AUGUSTUS, Meena [US/US]; 3215 Hollyhock Drive, Burtonsville, MD 20866 (US).
- (74) Agents: GRANT, Alan, J. et al.; Carella, Byrne, Bain, Gilfillan, Cecchi, stewart & Olstein, 5 Becker Farm Road, Roseland, NJ 07068 (US).

- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

of inventorship (Rule 4.17(iv)) for US only

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DETERMINING CANCER-LINKED GENES AND THERAPEUTIC TARGETS USING MOLECULAR CYTOGENETIC METHODS

(57) Abstract: Methods for identifying antineoplastic agents by using their ability to modify expression of specific genes or the biological activity of polypeptides encoded by such genes, wherein said genes are located in specific chromosomal regions, called amplicons, or regions of interest, and the presence of such amplified regions within a cancerous cell, are disclosed. Also described are methods for diagnosing cancerous, or potentially cancerous, conditions using these methods. Also encompassed are methods involving determining the modulated expression of the genes in these regions of interest (ROIs), or amplicons, as pharmacodynamic/pharmacogenetic/surrogate markers and/or for patient profiling prior to accrual for clinical trials/treatments based on the identification of these genes as validated gene/drug targets in various cancer tissue types.



DETERMINING CANCER-LINKED GENES AND THERAPEUTIC TARGETS USING MOLECULAR CYTOGENETIC METHODS

5

This application claims priority of U.S. Provisional Application Serial No. 60/550,304, filed 8 March 2004, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

15

20

10

The present invention relates to Identification of amplifications / gains of genomic segments of DNA within human chromosomes in diseased states, such as cancer, that are demarcated and limited within specific chromosomal bands and defined herein as "amplicons" and whose disruption and/or change in expression is useful to distinguish cancerous from non-cancerous tissue and serve as potential therapeutic targets, pharmacodynamic /pharmacogenetic/surrogate and prognostic and diagnostic markers.

25

BACKGROUND OF THE INVENTION

Malignant tumors are a leading cause of death in the United States and one in four Americans is likely to die of cancer. This disease is often characterized by an increase in the number of abnormal, neoplastic cells that are ultimately derived from a normal tissue after which the cells proliferate to form a tumor, which can then metastasize (spreading into adjacent tissues or traveling elsewhere in the body via the bloodstream or lymphatic system).

35

30

5

10

15

20

25

30

The genomes of various well-studied tumors carry several different independently altered genes, including activated oncogenes and inactivated tumor suppressor genes. Chromosomal abnormalities have been identified in most cancer cells. Conventional chromosome banding techniques allow for the detection of specific chromosomal defects in tumor cells but interpretation of the banding pattern is sometimes difficult, particularly when complex chromosomal rearrangements or subtle abnormalities are present. In recent years, new techniques, such as CGH and SKY, based on fluorescent in situ hybridization (FISH) (Pinkel et al., Proc Nat Acad Sci USA 85:9138-42 (1988)) have been developed to overcome the limitations of conventional chromosome banding. CGH measures intensities of fluorescently labeled tumor DNA and normal DNA following hybridization to normal chromosomes (Kallioniemi et al., Science 258:818-21 (1992)). Gain or loss of copy number of a particular chromosome or chromosome region in the tumor DNA is determined by the relative intensity of a fluorescence ratio. SKY utilizes a cocktail of chromosome probes, fluorescently labeled to specify each chromosome, which is hybridized to tumor chromosomes in an effort to identify numerical and structural abnormalities in the tumor cell (Schröck et al., Science 273:494-7 (1996)). CGH and SKY have been used to identify chromosomal regions that harbor genes significant to the process of tumor initiation or progression.

The identification of amplifications of genomic DNA within well defined and demarcated limits on human chromosomes is done at a resolution of human chromosome banding limited to 400-550 bands by the technique of Comparative Genomic Hybridization (CGH). The present invention applies custom protocols to obtain human template chromosomes that are resolved to 850 to 1000 band resolution of human chromosomes (ISCN, 1985), to perform CGH on a large number of cell lines/ tissue samples/tumor cells. This allows the identification of regions of genomic DNA amplifications ranging from 2-5 Mbp at the highest limits of resolution of human chromosomes, detected by fluorescent intensity evaluations performed at the microscope.

Amplicons, or regions of interest,, from 10-20 Mb and more are also defined by these methods. These amplicons contain a gene, or genes, that are amplified (meaning copy number gains), and/or differentially expressed in the tissue/ cells of origin. Genes identified as being amplified and/or over-expressed provide targets for intervention with a small molecular therapeutic, antibodies, anti-sense or other therapeutic modalities. A gene or genes within these regions could also be used for diagnostic or prognostic molecular pathology characterization and useful as pharmacodynamic biomarkers for drug response profiling and patient sub-set selection and stratification.

10

5

BRIEF SUMMARY OF THE INVENTION

In one aspect the present invention relates to a set of genes that have been localized within human chromosomal regions of interest (ROI) that have been identified by molecular cytogenetic techniques. In particular, the present invention relates to chromosomal regions of interest, or amplicons, that are summarized in Table 1 and containing genes corresponding to cDNA sequences shown in the sequence listing described herein.

20

25

15

In another aspect, the present invention relates to a method for diagnosing the presence of a cancerous condition, or diagnosing a predisposition to developing a cancerous condition, in an animal, especially a human being, by determining the amplification and/or over-expression, of one or more genes corresponding to SEQ ID NO: 1-3049 in a cell, or tissue sample, obtained from an animal. The animal may be afflicted with, or at risk of developing, such a cancerous condition, or otherwise predisposed to develop such a condition.

30

In a further aspect, the present invention relates to a method for the treatment of a cancerous condition, especially one involving breast, colon, lung, cervix, kidney, pancreas and prostate tissues, utilizing selected chemical

agents having anti-tumor activity as identified using one of the assays disclosed herein.

Thus, in one aspect the present invention relates to a method for identifying an antineoplastic agent, comprising:

- (a) contacting a test compound with a cell that expresses at least one gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 3049 and under conditions promoting expression of said gene; and
- (b) determining a change in expression of said gene as a result of said10 contacting

5

20

25

30

wherein a change in expression indicates gene modulation thereby identifying said test compound as a gene modulating agent. In a preferred embodiment thereof, the change in expression is a decrease in expression.

In a further aspect, the present invention relates to a method for identifying a compound as an anti-neoplastic agent, comprising:

- (a) contacting a test compound with a polypeptide encoded by a gene selected from SEQ ID NO: 1-3049,
- (b) determining a change in a biological activity of said polypeptide due to said contacting,

wherein a change in activity indicates anti-neoplastic activity and thereby identifies such test compound as an agent having antineoplastic activity.

Preferably, the change in biological activity is a decrease in biological activity. Also preferred is where the biological activity is an enzyme activity, most preferably involving an enzyme selected from kinase, protease, peptidase, phosphodiesterase, phosphatase, dehydrogenase, reductase, carboxylase. transferase, deacetylase and polymerase. Also preferred is a biological activity that is a membrane transport activity, an integrin, a Cytochrome P450 enzyme, a nuclear hormone receptor, or a receptor activity,

5

10

15

20

25

30

such as a G-protein-coupled receptor. In other preferred embodiments, the polypeptide is contained in a cell.

The present invention also relates to a method for treating cancer comprising contacting a cancerous cell with an agent first identified as having gene modulating activity using any of the methods of the invention and in an amount effective to cause a reduction in cancerous activity of said cell. In a preferred embodiment, said cancerous cell is contacted *in vivo*, as where the agent is administered to a mammal, especially a human being, afflicted with cancer and in an amount sufficient to ameliorate the cancer.

The present invention further relates to a method for treating cancer comprising contacting a cancerous cell with an agent having affinity for an expression product of a gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1-3049 and in an amount effective to cause a reduction in cancerous activity of said cell. Preferably, the expression product is a polypeptide and the agent is an antibody.

The present invention also relates to a method for monitoring the progress of cancer therapy in a patient comprising monitoring in a patient undergoing cancer therapy the expression of a gene corresponding to a polypeptide having a sequence selected from SEQ ID NO: 1-3049, preferably wherein the gene comprises a sequence of SEQ ID NO: 1-3049, such as where the cancer therapy is chemotherapy.

In a further embodiment, the present invention relates to a method for determining the likelihood of success of cancer therapy in a patient, comprising monitoring in a patient undergoing cancer therapy the expression of a gene corresponding to a polynucleotide having a sequence of one or SEQ ID NO: 1-3049 wherein a decrease in said expression prior to completion of said cancer therapy is indicative of a likelihood of success of said cancer

therapy, preferably wherein the gene comprises a sequence of SEQ ID NO: 1-3049 and wherein the cancer therapy is chemotherapy.

The present invention still further relates to a method for determining the progress of a treatment for cancer in a patient afflicted therewith, following commencement of a cancer treatment on said patient, comprising:

- (a) determining in said patient a change in expression of one or more genes corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1-3049; and
- (b) determining a change in expression of said gene compared to expression of said one or more determined genes prior to commencement of said cancer treatment;

wherein said change in expression indicates progress of said treatment thereby determining the progress of said treatment. Preferred embodiments include where the change in expression is a decrease in expression and said decrease indicates success of said treatment.

20 DEFINITIONS

5

10

15

25

30

As used herein, the following terms have the indicated definition unless expressly stated otherwise.

The term "amplicon" refers to regions of interest, i.e., genomic segments of DNA within human chromosomes in diseased states like cancer that are demarcated and limited within specific chromosomal bands. Since these amplicons contain sequences of a gene/ or genes that are amplified (copy number gains), and/ or differentially expressed in the tissue/ cells of origin, a listing of these genes within the amplicons detected are listed in Table 3. Genes identified as being amplified and/or over-expressed within the amplicons provide a useful target for intervention with small/large

molecule/protein/antibody therapeutics, anti-sense or other therapeutic modalities. A gene or genes within these regions is also useful for diagnostic or prognostic molecular pathology characterization/companion diagnostics, and useful as pharmacodynamic biomarkers for drug response profiling and patient sub-set selection and stratification.

The term "percent identity" or "percent identical," when referring to a sequence, means that a sequence is compared to a claimed or described sequence after alignment of the sequence to be compared (the "Compared Sequence") with the described or claimed sequence (the "Reference Sequence"). The Percent Identity is then determined according to the following formula:

Percent Identity = 100 [1-(C/R)]

15

20

25

30

10

5

wherein C is the number of differences between the Reference Sequence and the Compared Sequence over the length of alignment between the Reference Sequence and the Compared Sequence wherein (i) each base or amino acid in the Reference Sequence that does not have a corresponding aligned base or amino acid in the Compared Sequence and (ii) each gap in the Reference Sequence and (iii) each aligned base or amino acid in the Reference Sequence that is different from an aligned base or amino acid in the Compared Sequence, constitutes a difference; and R is the number of bases or amino acids in the Reference Sequence over the length of the alignment with the Compared Sequence with any gap created in the Reference Sequence also being counted as a base or amino acid.

If an alignment exists between the Compared Sequence and the Reference Sequence for which the percent identity as calculated above is about equal to or greater than a specified minimum Percent Identity then the Compared Sequence has the specified minimum percent identity to the Reference Sequence even though alignments may exist in which the

5

10

15

20

25

30

hereinabove calculated Percent Identity is less than the specified Percent Identity.

As used herein, the terms "portion," "segment," and "fragment," when used in relation to polypeptides, refer to a continuous sequence of residues, such as amino acid residues, which sequence forms a subset of a larger sequence. For example, if a polypeptide were subjected to treatment with any of the common endopeptidases, such as trypsin or chymotrypsin, the oligopeptides resulting from such treatment would represent portions, segments or fragments of the starting polypeptide. When used in relation to a polynucleotide, such terms refer to the products produced by treatment of said polynucleotides with any of the common endonucleases, or any stretch of polynucleotides that could be synthetically synthesized.

As used herein, the term "DNA segment" or "DNA sequence" refers to a DNA polymer, in the form of a separate fragment or as a component of a larger DNA construct, which has been derived from DNA, and may include both single stranded and duplex sequences. Such segments are provided in the form of an open reading frame uninterrupted by internal non-translated sequences, or introns, which are typically present in eukaryotic genes.

The term "coding region" refers to that portion of a gene which either naturally or normally codes for the expression product of that gene in its natural genomic environment, i.e., the region coding *in vivo* for the native expression product of the gene.

The term "nucleotide sequence" refers to a heteropolymer of deoxyribonucleotides. Generally, DNA segments encoding the proteins provided by this invention are assembled from cDNA fragments and short oligonucleotide linkers, or from a series of oligonucleotides, to provide a synthetic gene which is capable of being expressed in a recombinant

transcriptional unit comprising regulatory elements de rived from a microbial or viral operon.

The term "expression product" means that polypeptide or protein that is the natural translation product of the gene and any nucleic acid sequence coding equivalents resulting from genetic code degeneracy and thus coding for the same amino acid(s).

The term "fragment," when referring to a coding sequence, means a portion of DNA comprising less than the complete coding region whose expression product retains essentially the same biological function or activity as the expression product of the complete coding region.

15

20

25

30

10

5

DETAILED SUMMARY OF THE INVIENTION

The present invention relates to a set of genes that are amplified and/or over-expressed genes in cancer cell lines and have been localized to various chromosomal regions of interest. These genes have been identified through a combination of CGH, SKY, expression analysis and Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR). Such genes are both markers and potential therapeutic targets for cancer, in particular breast; colon, lung and prostate malignancies. In addition, the amplified nature of such genes provides a means of diagnosing a cancerous condition, or predisposition to a cancerous conditions, by determining the amplification of one or more of such genes in a patient afflicted with, or predisposed toward, or otherwise at risk of developing, cancer.

In one aspect the present invention relates to a set of genes that have been localized within human chromosomal regions of interest (ROI) that have been identified by molecular cytogenetic techniques. In particular, the present

invention relates to chromosomal regions of interest, or amplicons, that are summarized in Table 1. Table 2 lists tissues where the amplicons are found, cell lines expressing them, the amplification ratios found in those tissues for cancer versus normal cells, amplicon size and the chromosomal locations of the amplicons. Table 3 lists the chromosomal locations and accession number identifications of these regions of interest and which serve to correlate amplicons with the cDNA sequences of SEQ ID NO: 1-3049.

10 Table 1 - List of Amplicons

	AMPLICON	CHR	BPSTART	BPEND	BPLENGTH
15	A1 A2 A3 A4 A5 A6	8 13 5 13 7 10	122000000 96500000 175000000 26500000 101000000 73500000	127500000 100000000 181500000 34000000 106000000 82500000	5500000 3500000 6500000 7500000 5000000
20	A7 A8 A9 A10 A11	7 1 6 18 9	7100000 11650000 3600000 7050000 900000	77500000 120000000 4100000 76500000 18500000	6500000 3500000 5000000 6000000 9500000

For Table 1, CHR means chromosome number, BPLENGTH represents the number of nucleotides in the amplicon. BPSTART refers to "base pair start point" and BPEND refers to "base pair end point" along the chromosome based on the July 2003 human reference sequence UCSC version hg16 (NCBI Build 34).

30

25

5

Table 2. Amplicon Locations

			_		h		amplicon
cell line	Amp	tissue	chrom	band	band	Datio	size_MB
	#			start	stop	Ratio 14	5.3
HCC1954	A1	Breast	8	q24.13	q24.13		8.3
NCI_H446	A1	scLung	8	q24.13	q24.21	8	8.3
NCI_H827	A1	scLung	8	q24.13	q24.21	6	8.3
HCC202	A 1	Breast	8	q24.13	q24.21	6	5.3
NCI_H82	A 1	scLung	8	q24.13	q24.13	7	5.3
NCI_H23	A 1	nscLung	8	q24.13	q24.13	7	5.3 5.3
MDA MB436	A2	Breast	13	q32.2	q32.3	6	3.3
NCI H1963	A2	scLung	13	q32.3	q32.3	6	
EFM192A	A2	Breast	13	q32.3	q34	8	18.8
MDA MB157	A2	Breast	13	q32.3	q34	5	18.8
HCC1937	A2	Breast	13	q32.3	q32.3	4	3.3
SKBR3	A2	Breast	13	q32.3	q32.3	4	18.8
NCI H1963	A2	nscLung	13	q32.3	q32.3	6	3.3
HCC1954	A3	Breast	5	q35.3	q35.3	4	4.3
MDA MB436	A 3	Breast	5	q35.1	q35.3	7	14
BT20	A4	Breast	5	q35.1	q35.3	4	14
KPL1	A5	Breast	5	q35.1	q35.3	4	14
HCC3153	A6	Breast	5	q35.3	q35.3	3	4.3
HT29	A4	Colon	13	q12.3	q13.2	5	9
SW403	A4	Colon	13	q21.1	q21.2	15	6
BT20	A4	Breast	13	q12.3	q13.2	4	9
CPDR9	A4	Prostate	13	q12.2	q12.3	2	7.1
SW480	A5	Colón	7	q22.2	q22.2	9	_1
X71	A5	Colon	7	q22.1	q22.2	5	7.2
X72	A5	Colon	7	q22.3	q22.3	6	3.3
Lovo	A6	Colon	7	q22.1	q22.2	5	7.2
X1819 1	A7	Colon	7	q22.1	q22.2	5	7.2
EFM19	A6	Breast	10	q22.1	q22.3	6	15.3
PC3	A6	Prostate	10	q22.2	q22.3	7	8.'3
MDA MB436	A6	Breast	10	q22.1	q22.2	3	10.7
SKBR3	A6	Breast	10	q22.2	q22.3	4	8.3
SW48	A6	Colon	10	q22.1	q22.3	4	15.3
X71	A6	Colon	10	q22.2	q22.3	2	8.3
SKBR3	A7	Breast	7	q11.23	q11.23	5	4
X72	A7	Colon	7	q11.23		7	4
X72 X71	A7	Colon	7	q11.23		5	4
X1819_1	A7	Colon	7	q11.23		3 4	4
NCI H69	A7	scLung	7	q11.23			4
	A8	Breast	1	p12.2	p13.2		9
BT20	A8	Breast	1	p12	p12	6	6.7
CAMA-1	A8	Breast	1	p11.2	p13.3	11	14.7
KPL-1	A0 A9	Colon	6	p21.2	p21.2		3.4
Colo205		Breast	6	p21.1	p21.2		9.8
MDA_MB231	A9	Dieast	U	P2 1. 1	L	•	

NCIH522 PANC-1 NCI_H1607 NCI_H446	A9 A10 A11 A11	nscLung Pancreas scLung scLung Breast	6 18 9 9	p21.2 q23 p22.2 p22.3 p22.2	p21.31 q23 p23 p22.3 p23	6 7 10 8 10	9.1 5.2 14.5 2.9 14.5
HCC1954	A11	Breast	9	p22.2	p23	10	14.5

In addition, SEQ ID NO: 1-3049 represents the nucleotide sequences for cDNA sequences corresponding to genes located in these regions of interest. Such regions contain genes found to be amplified and over-expressed in cancerous tissues, especially of breast, colon, lung, cervix, kidney, pancreas and prostate.

Each amplicon may contain about 75 genes, at least one of which will be amplified in a cancerous condition. Genes that show amplification and/or over-expression can be indicative of the cancerous status of a given cell.

Briefly, the procedures used to identify the genes disclosed herein may be summarized as follows:

15

5

For CGH analysis, based on detailed molecular cytogenetic characterizations, the following data sets are generated, which may include regions reported in the public domain as well as unique regions not previously known.

20

1. A map of chromosomal regions involved in consistent, recurrent and high level genomic gains (i.e., amplifications) for a representative cancer cell line or tumor type (e.g. colon, prostate, breast and lung) that can be recognized as a pattern/signature for a given tumor type.

25

- 2. A map of chromosomal regions containing genomic losses (i.e., deletions) in each tumor type and individual cell line to be examined.
- 3. Levels of intensities of gains and losses categorized for entry into a database.

4. A comparison of the patterns of gains and losses between the clinical samples (e.g. colon xenografts) and cell lines (e.g., colon) of matched Stages and Grades.

5. A comparison of the patterns of gains and losses between primary prostate tumor cell lines (e.g., CPDR lines) and metastatic prostate tumor cell lines (e.g., DU 145, PC3 and LNCaP).

5

10

15

20

30

In accordance with the present invention, for SKY analysis, data sets were generated according to the following steps:

- 1. Identification and development of a database of novel chromosomal rearrangements in epithelial cancer cell lines.
- 2. Identification of novel translocations involving specific chromosomes or chromosomal regions
- 3. Reconciliation of SKY and CGH analysis on the same cell line as a verification of the combined findings.

Combining genomic DNA analysis of gains and losses in the tumor cell lines/clinical samples with cDNA expression analysis from matched tumor types displayed ordered on the assembled Human genome sequence :

- A pattern of gene expression on a Affymetrix chip set (U95 and U133)
 was used to generate differential gene expression profiles between
 samples sets containing normal and malignant tissues from colon,
 prostate, lung, breast and various cell lines.
- 25 2. A Spotfire™ visualization tool was developed that allowed the generation of a list of all the genes that are present in the Human genome sequence within the defined regions of gains/losses for each cell type/tumor type to identify genes to include in the HITS platform and for identification of cancer associated genes
 - 3. The following algorithm was employed:

PCT/US2005/007748

i) Match chromosomal regions of amplification/gains defined by CGH with the location of genes/ESTs on an Affymetrix chip as mapped to a Human genome template.

ii) Identify genes/ESTs over-expressed in tumor tissue compared to normal tissue in said chromosomal regions using.

iii) Compile data on cell lines of a particular tumor type and different tumor types showing clusters of genomic gains and losses at certain chromosomal regions.

iv) Pick BACs that span the chromosomal regions consistently gained and containing over-expressed genes in an effort to positionally clone novel cancer genes (oncogenes and genes in relevant pathways)

 Validate the identified genes by
 A) Picking STS markers that identify the gene sequence and quantify the relative copy number in genomic DNA and RNA across a panel of tumor cell lines.

B) Develop probes for FISH on chromosomes from tumor cell lines and primary tumor tissue micro-arrays.

4. The expression data from tumor cell lines that have undergone SKY/CGH analysis was used to pick candidate genes to validate as individual targets in functional genomic assays and in-vivo assays and for use in the transcriptional assay platform.

In accordance with the present invention, over-expression of cellular genes is conveniently monitored in model cellular systems using cell lines (such as is used in the example below), primary cells, or tissue samples maintained in growth media. For different purposes, these may be treated with compounds at one or more different concentrations to assay for modulating agents. Thus, cellular RNAs are isolated from the cells or cultures as an indicator of selected gene expression. The cellular RNAs are then divided and

10

5

15

20

25

30

5

15

20

25

30

subjected to analysis to determine the presence and/or quantity of specific RNA transcripts, which transcripts are then amplified for detection purposes using standard methodologies, such as reverse transcriptase polymerase chain reaction (RT-PCR). The levels of specific RNA transcripts, including their presence or absence, are determined. When used for identification of modulating agents, such as anti-neoplastic agents, a metric is derived for the type and degree of response of the treated sample compared to control samples.

In accordance with the foregoing, the amplicons identified as being amplified and/or over-expressed, which can include increased copy number thereof, in cancerous cells are localized in chromosomal regions of interest as identified in Tables 2 and 3.

The genes localized in these amplicons may be utilized to characterize, the cancerous, or non-cancerous, status of cells, or tissues. The methods of the invention may be used with a variety of cell lines or with primary samples from tumors maintained *in vitro* under suitable culture conditions for varying periods of time, or *in situ* in suitable animal models.

The amplicons disclosed herein are expressed at levels in cancer cells that are different from the expression levels in non-cancer cells. Expression in cancer versus non-cancer cells of the same tissue type is a key identifier.

In accordance with the forgoing, the present invention also relates to a method for identifying a gene modulating agent, such as an anti-neoplastic agent, comprising:

(a) contacting a test compound, a compound whose gene-modulating and/or anti-neoplastic activity is to be determined, with one or more cells expressing one or more genes mapped to the chromosomal region of interest, or amplicon, for genes as identified in Table 3, and

5

10

15

20

25

30

PCT/US2005/007748 WO 2006/033664 3

(b) determining a change in expression of said one or more genes compared to when said contacting has not occurred,

wherein a change in expression of said gene is indicative of gene modulating activity, thereby identifying said test compound as a gene modulating agent.

In accordance with the foregoing, the present invention relates to a method for identifying an antineoplastic agent, comprising:

- (a) contacting a test compound with a cell that expresses one or more amplicons of Table 2 having an amplification ratio of at least 2.0; and
- (b) determining a change in said amplification ratio due to said contacting;

wherein a change in said amplification ratio due to said contacting indicates that said test compound has gene modulating activity

thereby identifying said test compound as a gene modulating agent.

The present invention also contemplates a method for identifying an antineoplastic agent, comprising:

- (a) contacting a test compound with a cell that expresses at least one gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 - 3049 and under conditions promoting expression of said gene; and
- (b) determining a change in expression of said gene as a result of said contacting

wherein a change in expression indicates gene modulation thereby identifying said test compound as a gene modulating agent.

In preferred embodiments of these methods, the change in expression is a decrease in expression and/or the decrease in expression is a decrease in copy number of the gene and/or the gene comprises a nucleotide sequence of one of SEQ ID NO: 1-3049 and/or the cell was genetically engineered to express said gene.

5

10

15

20

25

30

Because the genes disclosed herein are over-expressed and relate to the cancerous condition of a cell, successful anti-neoplastic activity will commonly be exhibited by agents that reduce the expression of said genes in one embodiment thereof, the change in expression is a decrease in copy number of the gene or genes under study. In accordance therewith, said change in gene copy number is conveniently determined by detecting a change in expression of messenger RNA encoded by said gene sequence. In another preferred embodiment, expression is determined for more than one such gene, such as 2, 5, 10 or more of the genes.

Thus, the present invention also encompasses a method for detecting the cancerous status of a cell, comprising detecting elevated expression in said cell of at least one gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1-3049 whereby such elevated expression is indicative of cancerous status of the cell. In preferred embodiments thereof, the elevated expression is an elevated copy number of the gene.

Other methods useful in measuring a change in expression of the genes disclosed herein include measuring a change in the amount or rate of synthesis of a polypeptide encoded by said gene, preferably a decrease in synthesis of said polypeptide. Most preferably, the polypeptide comprises an amino acid sequence highly homologous to a sequence encoded by a gene mapping to an amplicon disclosed herein and whose expression is elevated in cancer.

The methods of the invention can thus be utilized to identify antineoplastic agents useful in treatment of cancerous conditions. Such activity can be further modified by first identifying such an agent using an assay as already described and further contacting such agent with a cancerous cell, followed by monitoring of the status of said cell, or cells. A change in status indicative of successful anti-neoplastic activity may include a decrease in the rate of replication of the cancerous cell(s), a decrease in the total number of progeny cells that can be produced by said cancerous cell(s), or a decrease in the number of times said cancerous cell(s) can replicate, or the death of said

1

WO 2006/033664

5

10

15

20

25

30

cancerous cell(s).

PCT/US2005/007748

Anti-neoplastic agents may also be identified using recombinant cells suitably engineered to contain and express the cancer-related genes disclosed herein. In one such embodiment, a recombinant cell is formed using standard technology and then utilized in the assays disclosed herein. Methods of forming such recombinant cells are well known in the literature. See, for example, Sambrook, et al., Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor, N.Y., (1989), Wu et al, Methods in Gene Biotechnology (CRC Press, New York, NY, 1997), and Recombinant Gene Expression Protocols, in Methods in Molecular Biology, Vol. 62, (Tuan, ed., Humana Press, Totowa, NJ, 1997), the disclosures of which are hereby incorporated by reference.

The present invention also relates to a method for detecting the cancerous status of a cell, comprising detecting elevated copy number and/or expression in said cell of at least one gene that maps to a chromosomal region of interest, or amplicon, as identified in Table 3. Such elevated expression may be readily monitored by comparison to that of otherwise normal cells having the same genes. Elevated expression of such genes is indicative of the cancerous state. Such elevated expression, including increased copy number, may be the expression of more than one such gene.

The present invention also relates to a method for detecting a cancerlinked gene comprising the steps of contacting a test compound, identified as having gene modulating activity for a gene mapping to one of the amplicons disclosed herein, with a cell expressing a test gene and detecting modulation, such as decreased activity, of such test gene relative to when said compound

is not present thereby identifying said test gene as a cancer-related gene. In preferred embodiments, the gene determined by said method is an oncogene, or cancer facilitating gene.

In another embodiment, there is provided a method for treating cancer comprising contacting a cancerous cell with an agent first identified as having gene modulating activity using any of the assay methods disclosed according to the invention and in an amount effective to reduce the cancerous activity of said cell. In a preferred embodiment, the cancerous cell is contacted *in vivo*. In other preferred embodiments, said reduction in cancerous activity is a decrease in the rate of proliferation of said cancerous cell, or said reduction in cancerous activity is the death of said cancerous cell.

The present invention further relates to a method for treating cancer comprising contacting a cancerous cell with an agent having activity against an expression product encoded by a gene mapping to an amplicon as disclosed herein, preferably where the expression product is a polypeptide. In a preferred embodiment, said cancerous cell is contacted *in vivo*. In another preferred embodiment, the agent is an antibody.

20

25

30

5.

10

15

Nucleotide sequences mapping to the amplicons disclosed herein may be genomic in nature and thus represent the sequence of an actual gene, such as a human gene, or may be a cDNA sequence derived from a messenger RNA (mRNA) and thus represent contiguous exonic sequences derived from a corresponding genomic sequence or they may be wholly synthetic in origin for purposes of testing. Such cDNA sequences, mapping to the amplicons disclosed herein are identified as SEQ ID NO: 1-3049.

As described in the Example below, the expression of cancer-related genes may be determined from the relative expression levels of the RNA complement of a cancerous cell relative to a normal (i.e., non-cancerous) cell. Because of the processing that may take place in transforming the initial RNA

5

10

15

20

25

30

transcript into the final mRNA, the sequences disclosed herein may represent less than the full genomic sequence. They may also represent sequences derived from ribosomal and transfer RNAs. Consequently, the genes present in the cell (and representing the genomic sequences) and the sequences disclosed in SEQ ID NO: 1-3049, which are mostly cDNA sequences, may be identical or may be such that the cDNAs contain less than the full genomic sequence. Such genes and cDNA sequences are still considered corresponding sequences because they both encode similar RNA sequences. Thus, by way of non-limiting example only, a gene that encodes an RNA transcript, which is then processed into a shorter mRNA, is deemed to encode both such RNAs and therefore encodes an RNA complementary to (using the usual Watson-Crick complementarity rules), or that would otherwise be encoded by, a cDNA (for example, a sequence as disclosed herein). Thus, the sequences disclosed herein correspond to genes contained in the cancerous or normal cells used to determine relative levels of expression because they represent the same sequences or are complementary to RNAs encoded by these genes. Such genes also include different alleles and splice variants that may occur in the cells used in the methods of the invention.

In addition, sequences encoding the same proteins as any of these genes, regardless of the percent identity of such sequences, are also specifically contemplated by any of the methods of the present invention that rely on any or all of said sequences, regardless of how they are otherwise described or limited. Thus, any such sequences are available for use in carrying out any of the methods disclosed according to the invention. Such sequences also include any open read ing frames, as defined herein, present within any genes mapping to the amplicons of the invention.

The present invention also finds use as a means of diagnosing the presence of cancer in a patient, as where a sample of cancerous tissue or cells, or tissues or cells suspected of being cancerous, are examined for elevated expression, such as at least 2 fold expression, of a gene in one of

the amplicons disclosed herein, such as an increased expression of a cDNA sequence, or polypeptide encoded by said cDNA sequence, disclosed in Table 3 and being one of the sequences of SEQ ID NO: 1-3049.

For such purposes, and in accordance with the disclosure elsewhere herein, such diagnosis is based on the detection of elevated expression or amplification, such as elevated copy number, of one or more of the genes identified according to the invention. Such elevated expression can be determined by any of the means described herein.

10

15

20

25

30

5

In one such embodiment, the elevated expression, as compared to normal cells and/or tissues of the same organ, is determined by measuring the relative rates of transcription of RNA, such as by production of corresponding cDNAs and then analyzing the resulting DNA using probes developed from genes mapping to the amplicons of the invention. Thus, the levels of cDNA produced by use of reverse transcriptase with the full RNA complement of a cell suspected of being cancerous produces a corresponding amount of cDNA that can then be amplified using polymerase chain reaction, or some other means, such as rolling circle amplification, to determine the relative levels of resulting cDNA and, thereby, the relative levels of gene expression.

For RNA analysis, the latter may be isolated from samples in a variety of ways, including lysis and denaturation with a phenolic solution containing a chaotropic agent (e.g., triazol) followed by isopropanol precipitation, ethanol wash, and resuspension in aqueous solution; or lysis and denaturation followed by isolation on solid support, such as a Qiagen resin and reconstitution in aqueous solution; or lysis and denaturation in non-phenolic, aqueous solutions followed by enzymatic conversion of RNA to DNA template copies. Steady state RNA levels for a given type of cell or tissue may have to be ascertained prior to employment of the methods of the invention but such

is well within the skill of those in the art and will not be further described in detail herein.

Alternatively, increased expression, such as increased copy number, may be determined for the genes present in a cancerous cell, or a cell suspected of being cancerous, by determining elevated expression within the regions of interest, or amplicons, disclosed herein. Thus, the DNA of such cells may be extracted and probed for increased gene expression within the area disclosed herein as amplified in different cancer types and tissues.

10

15

20

25

30

5

In employing the methods of the invention, it should be borne in mind that gene expression indicative of a cancerous state need not be characteristic of every cell found to be cancerous. Thus, the methods disclosed herein are useful for detecting the presence of a cancerous condition within a tissue where less than all cells exhibit the complete pattern of over-expression. For example, a set of selected genes, which are found within the regions of interest disclosed herein, may be found, using appropriate probes, either DNA or RNA, to be present in as little as 60% of cells derived from a sample of tumorous, or malignant, tissue while being absent from as much as 60% of cells derived from corresponding noncancerous, or otherwise normal, tissue (and thus being present in as much as 40% of such normal tissue cells). In a preferred embodiment, such gene pattern is found to be present in at least 70% of cells drawn from a cancerous tissue and absent from at least 70% of a corresponding normal, noncancerous, tissue sample. In an especially preferred embodiment, such gene pattern is found to be present in at least 80% of cells drawn from a cancerous tissue and absent from at least 80% of a corresponding normal, noncancerous, tissue sample. In a most preferred embodiment, such gene pattern is found to be present in at least 90% of cells drawn from a cancerous tissue and absent from at least 90% of a corresponding normal, noncancerous, tissue sample. In an additional embodiment, such gene pattern is found to be present in at least 100% of cells drawn from a cance rous tissue

5

10

15

20

25

30

and absent from at least 100% of a corresponding normal, non-cancerous, tissue sample, although the latter embodiment may represent a rare occurrence.

Because changes in expression of these genes (up-regulation) are linked to the disease state (i.e. cancer), the change in expression may contribute to the initiation or progression of the disease. For example, if a gene that is up-regulated is an oncogene such a gene provides for a means of screening for small molecule therapeutics beyond screens based upon expression output alone. For example, genes that display up-regulation in cancer and whose elevated expression contributes to initiation or progression of disease represent targets in screens for small molecules that inhibit or block their function. Examples include, but are not be limited to, kinase inhibition, cellular proliferation, substrate analogs that block the active site of protein targets, etc.

It should be noted that there are a variety of different contexts in which genes have been evaluated as being involved in the cancerous process. Thus, some genes may be oncogenes and encode proteins that are directly involved in the cancerous process and thereby promote the occurrence of cancer in an animal. Other genes may simply be involved either directly or indirectly in the cancerous process or condition and may serve in an ancillary capacity with respect to the cancerous state. All such types of genes are deemed with those to be determined in accordance with the invention as disclosed herein. Thus, the gene determined by said method of the invention may be an oncogene, or the gene determined by said method may be a cancer facilitating gene, the latter including a gene that directly or indirectly affects the cancerous process, either in the promotion of a cancerous condition or in facilitating the progress of cancerous growth or otherwise modulating the growth of cancer cells, either in vivo or ex vivo. Such genes may work indirectly where their expression alters the activity of some other gene or gene expression product that is itself directly involved in initiating or

facilitating the progress of a cancerous condition. For example, a gene that encodes a polypeptide, either wild or mutant in type, which polypeptide acts to suppress of tumor suppressor gene, or its expression product, will thereby act indirectly to promote tumor growth.

5

10

15

20

25

30

Many cancerous genes appear to have their effect by encoding an aberrant protein that functions in a cell in a manner different from that of normal cells, or else said protein is overproduced or underproduced as a result of some mutation in the coding sequence, or promoter or enhancer sequences, of a particular gene, such as one of Genes 1 – 3049 disclosed herein and expressed by the amplicons of the invention.

In accordance with the present invention, there are provided methods for measuring the activity, such as a biological activity, of such a polypeptide. Such biological activity may include any measurable activity, such as chemical reactivity, catalytic ability, binding to specific structures and receptors, acting as a receptor, or just being present in a membrane of a cell and therefore available as a target site for antibodies or other agents. Any such polypeptides may thus provide a target for a chemotherapeutic agent, especially an antineoplastic agent.

As is well known in the art, polypeptide activities can be measured in different ways so as to enable screening procedures for agents, such as test compounds, that inhibit the activity of the polypeptide and thereby work against the function of that polypeptide, such as where the polypeptide is some type of cancer-related protein, such as that produced by expression of an oncogene, or where the polypeptide is overproduced as part of the cancer initiating or facilitating process. As non-limiting examples, such screening methods for antineoplastic agents can include the measurement of compounds that bind to proteins (or that bind to a gene or a transcript of a gene), compounds that inhibit expression (including processing and/or maturation) of a protein, or the detection of downstream reaction product,

most often with specific antibodies using enzyme-linked immunosorbent assay (ELISA) procedures well known in the art, or compounds that inhibit activity, such as enzyme activity or some other function, or compounds that interact with upstream or downstream proteins (such as with transcription factors or other binding proteins that may serve to regulate gene expression).

5

10

15

20

25

30

In accordance with the foregoing, the present invention relates to a method for identifying a compound as an anti-neoplastic agent, comprising:

- (a) contacting a test compound with a polypeptide encoded by a gene selected from SEQ ID NO: 1 3049,
- (b) determining a change in a biological activity of said polypeptide due to said contacting,

wherein a change in activity indicates anti-neoplastic activity and thereby identifies such test compound as an agent having antineoplastic activity.

In a preferred embodiment, the change in biological activity is a decrease in biological activity.

In another preferred embodiment, the biological activity is an enzyme activity, such as where the enzyme is one selected from the group kinase, protease, peptidase, phosphodiesterase, phosphatase, dehydrogenase, reductase, carboxylase, transferase, deacetylase and polymerase.

for available, such as enzymes are Assays for these relevant pharmacologically phosphodiesterases (the most phosphodiesterases are those that hydrolyze cyclic nucleotides (see, for example, cAMP and cGMP assays available from Perkin-Elmer, as well as Estrade et al., Eur. J. Pharmacol. 352:2-3, 157-163 (1998)).

Protein phosphatases remove phosphate residues from proteins. Most tests of their activity use the same assays as for protein kinases. A non-radioactive phosphatase assay system is available from Promega Biotech.

The therapeutically most relevant dehydrogenases oxidize or reduce small molecular weight metabolites, esp. steroid hormones, or that generally use or generate NAD or NADP (see: Haeseleer et al., J. Biol. Chem., 273:21790-21799 (1998)). A commercial assay is available from Cayman Chemical (at www.caymanchem.com).

5

10

15

20

25

30

Gamma-carboxylases are important enzymes in the blood coagulation process. The main assay protocols use synthetic peptides (see: Ulrich et al., J. Biol. Chem., 263:9697-9702 (1988); Begley et al., J. Biol. Chem., 275:36245-36249 (2000)).

In highly preferred embodiments, the kinase is one of a protein kinase, a serine or threonine kinase, or a receptor tyrosine protein kinase. Where the polypeptide encoded by a gene of the invention is a protein kinase, especially involving tyrosine kinase, various assays for activity are available. Protein kinases add phosphate groups to serine, threonine or tyrosine residues on proteins, most commonly measured with phospho-serine, threonine, or tyrosine-specific antibodies, or generation of radiolabeled substrate, or consumption of ATP, or phosphorylation of (synthetic) small peptides, or measuring downstream enzyme activity and gene transcription. Such assays are commercially available. (See, for example, the tyrosine kinase assay from Roche Molecular Biochemicals). Assays for serine/threonine kinases are also available at Chromagen.com, Upstate Biotechnology, Inc. (Lake Placid, NY, and at upstatebiotech.com) and from Applied BioSystems (Foster City, CA (home.appliedbiosystems.com)).

In other specific embodiments, the protease is a serine protease, cysteine protease or aspartic acid protease, or the transferase is a methyltransferase, preferably a cytosine methyltransferase or an adenine methyltransferase, or the deacetylase is a histone deacetylase, or the

5

10

30

carboxylase is a γ -carboxylase, or the peptidase is a zinc peptidase, or the polymerase is a DNA polymerase or an RNA polymerase.

Proteases degrade proteins, un-specifically or at specific sites. Almost all pharmacologically relevant ones have very narrowly defined specific substrates, and their activity is most often measured by directly measuring cleavage product or generation of (fluorescent) light after cleavage of synthetic substrates. Assays are available for serine proteases (Calbiochem, Palo Alto, CA, and see Berdichevsky et al., J. Virol. Methods, 107:245-255 (2003), for systeine proteases (See: Schulz et al., Mol. Pathol., 51:222-24 (1998) and Selzer et al., PNAS, 96:11015-11022 (1999)), for aspartic acid proteases (Geno Tech, Inc. at www.genotech.com) and for zinc peptidases (see Evans et al., J. Biol. Chem., 278:23180-23186 (2003)).

Both (regulatory) DNA-methylases and (biosynthetic) protein methylases that are drug targets. (See: Jonassen and Clarke, J. Biol. Chem., 275:12381-12387 (2000); Jackson et al., Nature, 416:556-560 (2002)).

Most HDAC (histone deacetylase) assays use colorimetric or fluorometric (synthetic) substrates. Standard assays are for binding, especially molecular size changes, blocking a specific site, and effects on transcription or downstream reactions (if DNA or RNA is the direct target of a drug). A commercial assay is available from Vinci Biochem (at www.vincibiochem.it).

In another specific embodiment, the biological activity is a membrane transport activity, preferably wherein the polypeptide is a cation channel protein, an anion channel protein, a gated-ion channel protein or an ABC transporter protein. Drug effects on the activity of transporter and channel proteins are screened by measuring increase or decrease of the ((radio-)labeled) transported entity inside or outside the cell, in cell-based assays, ATP consumption (in the case of ATPases), or changes in cell membrane

potential. Assays employing such proteins are available, such as for ABC transporter (see: Marcil et al., Lancet, 354:1341-46 (1999) and for ion channels (from Evotec OAI, at www.evotecoai.com and from PharmaLinks, at www.pharmalinks.org/research/cellsignalling).

5

10

15

20

25

30

In one embodiment, the polypeptide is an integrin (the signal transduction pathways elicited by the integrins are slow and not very well characterized, hence most assays are either just binding assays or measure downstream biological phenomena (such as migration, invasion, etc.) (See: Ganta et al., Endocrinology, 138:3606-3612 (1997); Sim et al., J. Biomed. Mater. Research, 68A:352-359 (2004); and Weinreb et al., Anal. Biochem., 306:305-313 (2002)), or a Cytochrome P450 enzyme (almost all cytochrome assays require knowledge of what the substrate is and measure conversion of substrate (free or (radio-)labeled) or generation of product; useful C14-labeled **Biosciences** Amersham from available substrates are www1.amershambiosciences.com), or a nuclear hormone receptor (Assays available from Discoverx, Fremont, CA, such as an estrogen assay; also see Rosen et al., Curr. Opin. Drug. Discov. Devel., 6:224-30 (2003)).

In one preferred embodiment, the biological activity is a receptor activity, preferably where the receptor is a G-protein-coupled receptor (GPCR).

GPCRs are transmembrane proteins that wind 7 times back and forth through a cell's plasma membrane with a ligand binding site located on the outside of the membrane surface of the cell and the effector site being present inside the cell. These receptors bind GDP and GTP. In response to ligand binding, GPCRs activate signal transduction pathways which induce a number of assayable physiological changes, e.g., an increase in intracellular calcium levels, cyclic-AMP, inositol phosphate turnover, and downstream gene transcription (directly or via reporter-assays) along with other translocation assays available for measuring GPCR activation when the polypeptide

encoded by a gene of the invention is a GPCR. Thus, such proteins work through a second messenger. The result is activation of CREB, a transcription factor that stimulates the production of gene products. One useful assay is the so-called BRET2/arrestin assay, useful in screening for compounds that interact with GPCRs. (See: Bertrand et al, J. Recept. Signal Transduct Res., 22:533-41 (Feb.-Nov. 2002)). In addition, numerous assays are commercially available, such as the Transfluor Assay, available from Norak Biosciences, Inc. (www.norakbio.com) or ArrayScan and KineticScan, both from Cellomics, or assays from CyBio (Jena, Germany).

10

15

20

25

30

5

Assays useful with the invention are usually set up to screen for agonists or antagonists after adding ligand, but effects on most of these parameters can be measured whether or not the ligand for the receptor is known. Such assays may involve radioligand-binding assays. Activation of the majority of GPCRs by agonists leads to the interaction of beta-arrestin (a protein that is involved in receptor desensitization and sequestration) with the receptor, which is measurable by fluorescence energy transfer

The disclosure of all journal articles, or other publications, referred to herein are hereby incorporated by reference in their entirety.

In one embodiment, the polypeptide is in a solution or suspension and contact with the test compound is by direct contact between the test compound and the protein molecule. Alternatively, the polypeptide may be in a cell and the test compound may have to diffuse into the cell in order to contact the polypeptide. In an alternative embodiment, the test compound may be contacted with a cell that contains or expresses the polypeptide but the test compound may have no direct contact with the polypeptide. In stead, the test compound may act to induce production and/or activity of a different compound, such as an intracellular second messenger that serves to contact the polypeptide and modulate or change the biological activity of this polypeptide.

In accordance with the foregoing, the method of the present invention includes cancer modulating agents that are themselves either polypeptides, or small chemical entities, that affect the cancerous process, including initiation, suppression or facilitation of tumor growth, either *in vivo* or *ex vivo*. Such agents may also be antibodies that react with one or more polypeptides encoded by genes present in the amplicons of the invention.

In keeping with the disclosure herein, the present invention also relates to a method for treating cancer comprising contacting a cancerous cell with an agent having activity against an expression product encoded by a gene mapping within regions of chromosomal interest.

The method of the present invention includes embodiments of the above-recited method wherein said cancer cell is contacted *in vivo* as well as *ex vivo*, preferably wherein said agent comprises a portion, or is part of an overall molecular structure, having affinity for said expression product. In one such embodiment, said portion having affinity for said expression product is an antibody.

20

25

30

5

10

15

In one embodiment of the present invention, a chemical agent, such as a protein or other polypeptide, is joined to an agent, such as an antibody, having affinity for an expression product of a cancerous cell, such as a polypeptide or protein encoded by a gene related to the cancerous process, especially a gene mapping to an amplicon as disclosed herein in a specific embodiment, said expression product acts as a therapeutic target for the affinity portion of said anticancer agent and where, after binding of the affinity portion of such agent to the expression product, the anti-cancer portion of said agent acts against said expression product so as to neutralize its effects in initiating, facilitating or promoting tumor formation and/or growth. In a separate embodiment of the present invention, binding of the agent to said expression product may, without more, have the effect of deterring cancer

promotion, facilitation or growth, especially where the presence of said expression product is related, either intimately or only in an ancillary manner, to the development and growth of a tumor. Thus, where the presence of said expression product is essential to tumor initiation and/or growth, binding of said agent to said expression product will have the effect of negating said tumor promoting activity. In one such embodiment, said agent is an apoptosis-inducing agent that induces cell suicide, thereby killing the cancer cell and halting tumor growth.

5

10

15

20

25

30

Many cancers contain chromosomal rearrangements, which typically represent translocations, amplifications, or deletions of specific regions of genomic DNA. A recurrent chromosomal rearrangement that is associated with a specific stage and type of cancer always affects a gene (or possibly genes) that play a direct and critical role in the initiation or progression of the disease. Many of the known oncogenes or tumor suppressor genes that play direct roles in cancer have either been initially identified based upon their positional cloning from a recurrent chromosomal rearrangement or have been demonstrated to fall within a rearrangement subsequent to their cloning by other methods. In all cases, such genes display amplification at both the level of DNA copy number and at the level of transcriptional expression at the mRNA level.

In accordance with the present invention, said functionally related genes are genes modulating the same metabolic pathway or said genes are genes encoding functionally related polypeptides. In one such embodiment, said genes are genes whose expression is modulated by the same transcriptional activator or enhancer sequence, especially where said transcriptional activator or enhancer increases, or otherwise modulates, the activity of a gene mapping to one of the amplicons of the invention.

The present invention also relates to a process that comprises a method for producing a product, such as test data, comprising identifying an

5

10

15

20

25

30

agent according to one of the disclosed methods for identifying such an agent (i.e., the therapeutic agents identified according to the assay procedures disclosed herein) wherein said product is the data collected with respect to said agent as a result of said identification process, or assay, and wherein said data is sufficient to convey the chemical character and/or structure and/or properties of said agent. For example, the present invention specifically contemplates a situation whereby a user of an assay of the invention may use the assay to screen for compounds having the desired enzyme modulating activity and, having identified the compound, then conveys that information (i.e., information as to structure, dosage, etc) to another user who then utilizes the information to reproduce the agent and administer it for therapeutic or research purposes according to the invention. For example, the user of the assay (user 1) may screen a number of test compounds without knowing the structure or identity of the compounds (such as where a number of code numbers are used the first user is simply given samples labeled with said code numbers) and, after performing the screening process, using one or more assay processes of the present invention, then imparts to a second user (user 2), verbally or in writing or some equivalent fashion, sufficient information to identify the compounds having a particular modulating activity (for example, the code number with the corresponding results). This transmission of information from user 1 to user 2 is specifically contemplated by the present invention.

In accordance with the foregoing, the present invention relates to a method for producing test data with respect to the anti-neoplastic activity of a compound, such as a test compound as defined herein, comprising:

- (a) identifying a test compound as having anti-neoplastic activity using a method of the invention, such as measuring the biological activity of a polypeptide encoded by a gene of Table 3 (SEQ ID NO: 1-3049), and
- (b) producing test data with respect to the anti-neoplastic activity of said test compound sufficient to identify the chemical structure of said test compound.

In another embodiment, the present invention provides a method for monitoring the progress of a cancer treatment, such as where the methods of the invention permit a determination that a given course of cancer therapy is or is not proving effective because of an increased or decreased expression of a gene, or genes, mapping to an amplicon as disclosed herein. For example, where there is an increased copy number of one or more of said genes monitoring of such genes can predict success or failure of a course of therapy, such as chemotherapy, or predict the likelihood of a relapse based on elevated activity or expression of one or more of these genes following such course of therapy.

In accordance with the foregoing, the present invention contemplates a method for determining the progress of a treatment for cancer in a patient afflicted with cancer, following commencement of a cancer treatment on said patient, comprising determining in said patient a change in expression of one or more genes, preferably more than one, corresponding to a gene of Table 3 or encoding a polypeptide or transcript of such a gene, or genes compared to expression of said one or more determined genes prior to commencement of said cancer treatment, wherein a change in expression, especially a decrease in expression, indicates positive effects of such treatment, thereby determining the progress of said treatment.

In a preferred embodiment, the detected change in expression is a decrease in expression. In another preferred embodiment, the cancer treatment is treatment with a chemotherapeutic agent, especially an agent that modulates, preferably decreases, expression of a gene identified herein, such as where said agent was first identified as having anti-neoplastic activity using a method of the invention. Thus, in accordance with this aspect of the present invention, a patient, or even a research animal, such as a mouse, rat, rabbit or primate, afflicted with cancer, including a cancer induced for research purposes, is introduced to a cancer treatment regimen, such as

5

10

15

20

25

30

administration of an anti-cancer agent, including one first identified as having anti-neoplastic activity by one or more of the screening methods disclosed herein. The progress and success or failure of such treatment is subsequently ascertained by determining the subsequent expression of one or more, preferably at least 3, or 5, or 10, of genes mapping to one or more of the amplicons disclosed herein, preferably to the same amplicon, or that encodes a transcript or polypeptide of such a gene following said treatment. In a preferred embodiment, a treatment that reduces said expression is deemed advantageous and may then be the basis for continuing said treatment. The methods of the invention thereby provide a means of continually monitoring the success of the treatment and evaluating both the need, and desirability, of continuing said treatment. In addition, more than one said treatment may be administered simultaneously without diminishing the value of the methods of the invention in determining the overall success of such combined treatment. Thus, more than one said anti-neoplastic agent may be administered to the same patient and overall effectiveness ascertained by the recited methods.

In accordance with the foregoing, the present invention also contemplates a method for determining the likelihood of survival of a patient afflicted with cancer, following commencement of a cancer treatment on said patient, comprising determining in said patient a change in expression of one or more genes, preferably more than one, corresponding to a gene of Table 3 or encoding a polypeptide or transcript of such a gene, or genes, compared to expression of said one or more determined genes prior to commencement of said cancer treatment, wherein a change in expression, es pecially a decrease in expression, indicates positive and life-extending effects of such treatment, thereby determining the likelihood of survival of said treatment.

In a preferred embodiment, the detected change in expression is a decrease in expression and said determined gene, or genes, may include 2, 3, 5, 10 or more of the genes described herein. Thus, the methods of the invention may be utilized as a means for compiling cancer survival statistics

following one or more, possibly combined, treatments for cancer as in keeping with the other methods disclosed herein.

The genes of the amplicons, or regions of interest, identified herein also offer themselves as pharmacodynamic markers (or as pharmacogenetic and/or surrogate markers), such as for patient profiling prior to clinical trials and/or targeted therapies, including combination treatments, resulting from the identification of these genes as valid gene targets for chemotherapy based on the screening procedures of the invention. In one embodiment thereof, the likelihood of success of a cancer treatment with a selected chemotherapeutic agent may be based on the fact that such agent has been determined to have expression modulating activity with one or more genes identified herein, especially where said genes have been identified as showing elevated expression levels in samples from a prospective patient afflicted with cancer. Methods described elsewhere herein for determining cancerous status of a cell may find ready use in such evaluations.

It should be cautioned that, in carrying out the procedures of the present invention as disclosed herein, any reference to particular buffers, media, reagents, cells, culture conditions and the like are not intended to be limiting, but are to be read so as to include all related materials that one of ordinary skill in the art would recognize as being of interest or value in the particular context in which that discussion is presented. For example, it is often possible to substitute one buffer system or culture medium for another and still achieve similar, if not identical, results. Those of skill in the art will have sufficient knowledge of such systems and methodologies so as to be able, without undue experimentation, to make such substitutions as will optimally serve their purposes in using the methods and procedures disclosed herein.

30

25

5

10

15

20

The present invention will now be further described by way of the following non-limiting example. In applying the disclosure of the example, it

should be kept clearly in mind that other and different embodiments of the methods disclosed according to the present invention will no doubt suggest themselves to those of skill in the relevant art.

5

10

15

20

25

30

EXAMPLE

Cancerous cells that over-express one or more genes mapping to the amplicons disclosed herein, are grown to a density of 10⁵ cells/cm² in Leibovitz's L-15 medium supplemented with 2 mM L-glutamine (90%) and 10% fetal bovine serum. The cells are collected after treatment with 0.25% trypsin, 0.02% EDTA at 37°C for 2 to 5 minutes. The trypsinized cells are then diluted with 30 ml growth medium and plated at a density of 50,000 cells per well in a 96 well plate (200 μl/well). The following day, cells are treated with either compound buffer alone, or compound buffer containing a chemical agent to be tested, for 24 hours. The media is then removed, the cells lysed and the RNA recovered using the RNAeasy reagents and protocol obtained from Qiagen. RNA is quantitated and 10 ng of sample in 1 μ l are added to 24 μI of Taqman reaction mix containing 1X PCR buffer, RNAsin, reverse transcriptase, nucleoside triphosphates, amplitaq gold, tween 20, glycerol, bovine serum albumin (BSA) and specific PCR primers and probes for a reference gene (18S RNA) and a test gene (Gene X). Reverse transcription is then carried out at 48°C for 30 minutes. The sample is then applied to a Perlin Elmer 7700 sequence detector and heat denatured for 10 minutes at 95°C. Amplification is performed through 40 cycles using 15 seconds annealing at 60°C followed by a 60 second extension at 72°C and 30 second denaturation at 95°C. Data files are then captured and the data analyzed with the appropriate baseline windows and thresholds.

The quantitative difference between the target and reference genes is then calculated and a relative expression value determined for all of the samples used. This procedure is then repeated for each of the target genes in

a given signature, or characteristic, set and the relative expression ratios for each pair of genes is determined (i.e., a ratio of expression is determined for each target gene versus each of the other genes for which expression is measured, where each gene's absolute expression is determined relative to the reference gene for each compound, or chemical agent, to be screened). The samples are then scored and ranked according to the degree of alteration of the expression profile in the treated samples relative to the control. The overall expression of the set of genes relative to the controls, as modulated by one chemical agent relative to another, is also ascertained. Chemical agents having the most effect on a given gene, or set of genes, are considered the most anti-neoplastic.

SEQUENCE LISTING ON CD-ROM ONLY

15

20

10

5

The sequences disclosed herein as SEQ ID NO: 1-3049 in the sequence listing are contained on compact disc (CD-ROM) only (denoted as Filename: Avalon 237 (5,279 kB), 4 copies of which appear on discs denoted Copy 1, Copy 2, Copy 3 and CRF, and which discs were generated on 7 March 2005), which accompanies this application and the contents of said CD-ROMs are hereby incorporated by reference in their entirety. These sequence numbers correspond to cDNA sequences derived from the genes identified in Table 3.

Table 3−/ Amplicon	Table 3 — Amplicon Identification Amplicon Transcript Id	Name	Chromosome	bpstart	pbend
A1	ENST00000303924	HAS2	ω	2582	259816
7. Z	00004	ι.	ω	58593	122609941
74. 14.	0000466		&	260852	122610061
73± D 1			Φ	122640599	265339
73. D 1	\sim		Φ	73811	373895
7.7.T	0000		ω	75017	392021
7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.	314393	NM 014943	_∞	75057	2394333
17. 1.0	ENSEST#000047109	l	ω	78972	379035
7.T.	00004711		∞	9218	2394333
777	00004711		&	123983935	398
7.7 L.V	00004711		&	98393	401120
T K	00001711		∞	2398	401120
T F	259512	NM 024295	80	123984034	01108
7. K	FNSESTTO000047115		8	123984041	990
A1	00001711		8	2398768	39995
71 71	00004711		∞	23	40112
7.T	00006561		8	124041564	124062478
A1	287380	NM 145647	∞	124041598	2412076
114	ENSESTT00000065617	ì	80	404207	2406621
7.7.7 V 1	309336	Q8TAK7	8	2404606	2409803
177	(r)	Q8TAK7	∞	4	407302
7 F	,	ì	8	124074181	
AL 8	00000551		ω	124094878	124098018
AT 77			&	124099026	124120
7.7.	000006562		8	124109587	12412098
AI	2000000		000	124109691	12412098
Al	ENSESTT00000005622		,)))	

124147875 124177793	124151533 124162903	124151533 124177809	685 1241	124188795 124210200	124188931 124210174	124189023 124210138	1195324 12421013	4218685 12423612	4222153 12422477	4224524 12424308	4224572 12424310	4284858 12428523	24289962 12436518	4294833 12431505	24305201 1243138	24315497 12432845	24369449 12437049	4385553 1	438555	601 1	4385602 124	4385602 124	124471947 124510034	124472004 124500973	マ	45100	4614600 1246	124614651 124621727	124614654 124621727
ω	œ	8	ω	ω	8	80	80	∞	∞	∞	∞	∞	∞	œ	∞	œ	∞	∞	ω	∞	∞	ω	ω	8	∞	∞	∞	∞	æ
086UY5	1		NM 032899	1	NM 032847	l			ZHX1				NM 014109	i				M 018024	ì				FBX032						
FNST00000318462	9000	ENSESTT00000065623	5699	000	767	0000	ENSESTT00000065673	ENSESTT00000065668	29785	0000	90	ENST00000309019	ω	9000	ENSESTT00000065667	\mathcal{Q}			900	9	000656	00065	28739	9000	00006566	0000656	2599	33005	2958
A1	A1	A1	A1	A1	A1	Al	Al	A1	A1	A1	A1	A1	A1	A1	A1	Al	A1	A1	A1	A1	A1	A1	Γ Δ	A1	A1	. Δ	77. 	77T	A1

124649681 124657768 124650068 124681581 124662584 124706220 124667216 124706214	124737531 124744075 124747485 124784276 124749308 124767066 124753384 124767066 124777101 124779458 124934987 124955009	24982464 1 25004837 1 25014902 1 25045027 1 25120753 1	25280819 12534151 25282330 12529625 25419757 12542110 25441637 12544318 25443596 12545522	125443702 125456727 125454689 125456214 125457337 125491832 125457337 125507878 125457337 125507907 125457337 125507908 125457337 125507913 125457339 125507908 125457339 125507908
ထထထထ	& & & & & & & & & & & & & & & & & & &	ထ ထ ထ ထ ထ	ထထထထထ	ထ ထ ထ ထ ထ ထ ထ ထ ထ ထ
ANXA13	Q8N6F3 NM_144963	NM_173684 NM_182525	× H	RNF139
ENSESTT0000065661 ENST00000262219 ENSESTT0000065659 ENSESTT0000065660	705 963 0656 0656 0656	39 39 04 161 10 10	ENST00000297632 ENSESTT00000049470 ENST00000328599 ENSESTT00000049469	ENSESTT0000049468 ENSESTT0000049466 ENSESTT0000049464 ENSESTT0000049463 ENSESTT0000049461 ENSESTT0000049461 ENSESTT0000049467 ENSESTT0000049467 ENSESTT0000049467
A1 A1 A1	A1 A1 A1 A1	A1 A1 A1	A1 A1 A1 A1	A1 A1 A1 A1 A1 A1

25472748 12550787 5472748 125507917 5473099 125507917 5507932 12551880	25519619 1256972 255219619 1256972 25521907 1255246 25525191 1255267	2553967 125697188 25668151 12569718 25942128 12594821 25965815 12596702	968234 1259907 974452 1259896 987460 1259910 993091 1259975 993091 1260015	25993448 12605272 26001094 12601293 26001094 12601293 26001094 12601353 26001094 12603240 26001094 12603240 26001148 12600873 26006063 12601353 26012674 12601610
[∞] ∞ ∞ ∞ °	ာ ထာ ထာ ထာ ထ	ာထထထထ	ထ ထ ထ ထ ထ ထ	0 & & & & & & & & & & & & & & & & & & &
NDUEB9	MTSS1	NM_152412	SQLE	Y196_HUMAN
0494(4945)	0494 064 0494 0494	049453 049453 04945 286 04945	89 04 04 04 04	04944 110 05295 05294 05294 05294 05295 05295
A1 A1 A1 A1	A1 A1 A1	A1 A1 A1 A1	A A 11 A	A1 A1 A1 A1 A1 A1 A1

, , t	000529		œ α	176 86	126043900
ENSESTIO000	.00000052941 .00000052942		0 00	6051717	2606057
ENST00000287	1437	NM 173685	∞	6060684	
ENSEST	05292	l	∞	6060694	2612011
ENSESTT0000	T00000052935		ω	26060694	2615140
ENSES	LT00000052934		∞	26060694	2632614
ENSES	293		ω	260	665
ENSES	0529		∞	260	632665
ENSES	293		ω	260	2665
ENSES	005292		ω	260606	633595
ENSES	0.005293		8	126060694	633595
ENSE	0005292		8	2606071	61514
ENSE	00529		æ	2606071	632665
ENSE	05292		∞	\sim	2633595
ENSE	005292		∞	2606074	2615140
ENSE	STT00000052925		∞	506074	2632665
ENSE	STT000005292		ω	261509	633595
FNSE	000529		∞	263170	632024
FNSE	0005292		∞	2632653	33292
ENST	11922	NM 025195	∞	39945	264072
ENSE	0005	1	ω	126399454	640486
FNSF	0005293		∞	264000	64023
FNSF	0005293		8	2640	640528
FNST	11709	09P1E1	ω	126552574	5359
FNGF	0005	ı	&		691977
FNST	2959		8	2704142	70430
FNCF	0000		ω	127466983	127469137
F N N N N N N N N N N N N N N N N N N N	0004666		ω	127487532	
ENSE	00004036		13	96395910	96638676

49 55	ത	α	828	5774	52	54	49	49	49	29	04	\sim	75	6357	96786095	986	681681	~	692711	681069	316	682518	682523	692735	96927359	96872107	96814040	96869522
ر ون	67	5 968000	67	S	0 96527	CO	5 96527	8996	8996	9676	673	9676	3 9677	5 9678	999	6789051	6800456	6800456	800456	6802878	802878	6802878	6802878	6802878	6802878	80	9195089	6806237
9649343 96493435	96493435	649343	649350	652604	604	652642	653	268199	7913	1564	3461	5432	9675959	9678148	96	96	96	96	96	96	896	96	96	96	96	96		90
															13	13	13	13	13	13	13	13	13	13	13	13	13	13
13 13	13	13		13	13	13	13	13	13		13	13	13	13	, - 1													
FARP1-006		FARP1-001	FARP1		bA10G5.1-002	bA10G5.1-001	ZNF183L1	.2-00	bA261P24.2-001		FARP1-002	EARP1-003	FARP1-004	FARP1-005	bA111L24.3-00		STK24-005	TK24	-00							STW24	STK24-006	STK24-003
ENSESTT00000040357		28	, 2		283	283			283	03	28	284	284	0284	284	035	286	2 00	020 0285	036	980	2 6	3 6	980	2 6	2	- C	0286
A2 A2	. 64	24	A2	C №	A2	712 A 2	A2	A2	A2	A2	A2	715 A2	2 Z	74 7.0	7 K	2 C	74 C k	AZ CK	74 c	AZ CK	74 C k	74 k	A K	AZ C	A2	AZ 4.0	AZ C	A2 A2

ŗ

A2 A2	6 3	STK24-004	13 13	8120: 2511	52 19
A2		STK24-007	13	552	4
A2	36		13	5528	45
A2	ENST00000313290	Q8WYY0	13	8685	24
A2	85	17.5-	13	2749	96929085
A2.	OTTHUMT00013002872	bA295B17.2-001	13	6054	133
A2	87	7.3-0	13	7993	96980244
A2	87	00	13	9106	49
A2	87	SLC15A1-001	13	3405	90
A CA	ENST00000218552	SLC15A1	13	97034979	82
A2	OTTHUMT00013002879	SLC15A1-002	13	17078	82
A2	ENST00000313260	014496	13	1111	375
A2	00289	55N3.2-	13	4374	0.4
A2	30028	bA155N3.2-001	13	4374	124
A2	49		13	4424	51
A2	04		13	4424	$\overline{}$
A2	0	DOC9 HUMAN	13	14736	999
82	290	$bA15\overline{5}N3.2-013$	13	97150543	111
A2	29	5N3.2-01	13	15791	\sim
A2	289	bA155N3.2-009	13	_	193
A2	049		13	16044	372
A .	049		13	16051	204
Z Z	290	3.2 - 01	13	16051	375
715 72	$\frac{1}{289}$	55N3.2-0	13	18165	97206239
77	289	55N3.2-00	13	18202	720033
20 20	288	3.3-00	13	18233	718488
2c1	280	55N3.2-00	13	19620	721073
77	049		13	20	97213319
A2	285	bA155N3.2-008	13	21043	721380

	723894 727134	72	43688	070	\sim	43664	43658	752474	754124	97541237	755	155096	755	3557	173579	3668	1830	ω	l C	9082	5447	97718142	366	7594	113668	73
$\sim \sim \sim$	39 25	2532	27230	\sim	30001	30569	30	97523848	54083	97541028	4669	54669	54765	55102	55102	97551031	55108	55108	55110	55114	55114	5	551	5	55117	5
13 13 13	13 13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
	bA155N3.2-004		bA155N3.2-002		bA318G11.2-001	bA155N3.2-003		bA122A8.3-001	bA122A8.1-001		bA87L10.1-001	DA87L10.1-002		1-00	7					1-00	$\overline{}$		bA178C10.1-001	•		PHGDHL1
ENSESTT00000040490 ENSESTT00000040489	1 00 4	48	300289		THUMT000130028	300289	4	88	∞	ENST00000325317	OTTHUMT00013002916	OTTHUMT00013002917	4	9	9	4	Ţ,	43	4	294	294	044	293	29	044	
A2 A2	A2 A2	A2	A2	A2	A2	A2	A2	A2	A2	A2	A2	A2	A A	A2	8	A2	A2	A2	A2	A 2	A 2	77	75 72	77	77	A2

1 97566117	756601	773	899	97611999	9760864	9760861		9760861	9765770	9765	9765770	9773564	9773668	9773595	9766921	9770228	9772782	9772294	3667	75908	6 97759317	784275	2 97851307	0 97897704	0 97905912	_	0 97913646	9791	786
9756523	97565627	758868	97594770	97604987	60499	60555	760583	97606624	97644794	97644799	97645785	97658207	97663038	97664963	340	191	97718042	\sim 1	530	775620	303	784153	9784998;	9785167	9785167	9785167	85167	785167	70517
13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	7 6) (
ba461N23.2-001		PHGDHL1	bA178C10.1-003	GPR18-001	GPR18		GPR18-002		EBI2-001	EBI2		bA178C10.1-006	bA178C10.1-004	DA178C10.1-005	-00	3.6-	0.1-00	3C10.			bA178C10.3-001	•	F16.2-00					•	
OTPHINE OF 13002920	5202		OFFHINTO0013002934	292		000	292	048	292) 	040	293	293	300293	0292	0292	0293	0295	40		7505	9660	3 5		F 0 5	7 5	יינ פייני	4040	ENSEST.TOOOOO404039
ر د	74 C/E	75	200	20	7 E	24 C 4	75 70	20	24 C 4	2 C E	200	200	76	3 6	20 0	25.	20 2	2 C K	7 C	7 6	AZ C	44 k	77 6	AZ G.F.	AZ F	AZ	AZ	A2	A2

TABLE 3 (Continued)

98125544 98215493 98215493 98242825 98242825	824314 824314 824314	186 186 216	832217 833701	33		833	833572	833574	98336159 98336160	98378429 98413856	866011	888068	601
98124280 98209116 98209116 98213298 98215060	165 165 165	232	3154	3323	3345	98334944	33504	33519	98335749 98335749	98378024	843933	43933	8439
13 13 13 13	13 13 13	13 13 13	13	13	13 13	13) ET F	13 13	13	113	13	13	13
bA134015.2-001 CLYBL-004 CLYBL-005	CLYBL-007	CLYBL-006 bA12G12.1-001	ZIC5 ZIC2-001	ZIC2	ZIC2-002	ZIC2-004	ZIC2-005		ZIC2-003	bA12G12.3-001	•	PCCA-001	
OTTHUMT00013002978 OTTHUMT00013002983 OTTHUMT00013002984 ENSESTT00000040311	⊣∞⊣	$\infty \vdash \subset$	7294 300299	5	20	0	2 0	ENSESTT00000040318 ENSESTT00000040319	OTTHUMT00013002996	\sim \sim	OTTHUMIOUT3003008 FNSESTT0000040321	സ	ENSESTIOU000040322 ENSESTIO0000040323
A2 A2 A2 A2 A2	A2 A2 A2	A2 A2 A2	A2 A2	A2 A2	A2	A2	A2 A2	A2 A2	A2	A2	AZ A	A2	A2 A2

988905 189 9902517 189 9902517	955249 989890 975664 989878 975708 989868	175708 9899256	976035 9898786	985320	992500 9901457	9006632 9902508	013216 9902506	018487 9902099	0018833 9902513	0018834 9902513	9018996 9902099	9058580 9940963	9106806 9910731	9106812 9910731	9111961 9911233	9291117 99294619	75066018 1/509144	75091160 17509223	75204533 17528815	75288871 17528	75289858 17529031	75367459 17537620	75414077 175415
13 13	13 13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	വ	Ŋ	5	ഹ	S	2	ഗ
근근	281	bA113J24.1-003	0011.	bA113724.1-006	00 - T • #					1.1-00	.1-0	5.1-00	5.2-00		Q9BXE6	bA118F16.1-001		HRH2	CPLX2	LNN960	08N9L3	THOC3	
2453 1300 1300	ENST00000245302 ENSESTT00000040332 ENSESTT00000040334	303	പ ഗ	JMT0001300304	א) ני	4030	030	000004030	4030	304	300304	30030	30030	0576	10	9080	ENSESTT00000026233	83		: :	101/2000011 101/2000011	255C	33
A2 A2 A2	A2 A2 A2	AZ	A2 A2	A2	A2	7 A	A2	A2	A 2	A2	A 2	A2	A S	A 2	A2	A2	A3	Z Z	C4 K	ָרָר אַ מַרָּ	C F	CA .	A3

75414077 1754152 5414083 1754152 5492772 1755174 5492798 1755048 5514024 1755288 5531948 1755380 5532319 1755342 5646358 1756978	5671357 17575391 5671357 17575391 57102967 17575392 5714285 17571465	75721351 17575337 75753991 17576966 75755867 17576203 75758565 17576362	75773428 17578142 75773498 17577689 75791865 17579651 75795923 17579768	5800471 17582446 5800698 17582428 5800698 17582428 5800716 17582446 5856279 17590492	75856301 175 75856353 175 75907924 175
א טטטטטטט ט	വവവറ	លលលល	មាយបាយ	വവവവവവ	សលស
Q8TBX6	Q8NDZ2	Q81Z15 NM_020444	_17366. B7_HUM_	CLTB NM_001834	NM_014613
ST00000331171 ST00000330220 ST00000253490 SESTT000000262 SESTT000000262 SESTT000000262	23	7 2 2 2 2 2	ST0000310389 SESTT000002624 ST0000327101 SESTT000002624	ENST000002/4/8/ ENSESTT0000026253 ENST0000310407 ENSESTT0000026254 ENSESTT0000026246	ST00000261942 SESTT0000002624 SESTT0000002624
A3 A3 A3 A3 A3 A3	A3 A3 A3	A3 A3 A3	A3 A3 A3	A3 A3 A3 A3	A3 A3 A3

75934638 175	5957282 17598306	5957315 17600359	986469 17599246	5994575 17	5994607 17600069	6003728 1760180	6004664 17600776	028134 17603789	76051522 1760539	052504 17605406	76055391 17606697	76055433 17606405	055433 17606575	76055433 1760657	6055504 17606071	76055510 1760640	5510 176065	76055510 1760657	76055540 1760648	6059752 17606556	76062303 17606562	6270544 17628232	6276066 17627834	81909 17628781	81927 17628551	6288997 17630	13206 17637761	6313206 176390	176
ιc) L	Ŋ	Ŋ	ß	S	S	2	Ŋ	വ	വ	ល	ഹ	S	5	ιΩ	J.	3	J.	Ŋ	Ŋ	ഹ	5	D.	5	2	5	S	Ŋ	S
RNF44	E E TATA	NM 017675	I			NM 052899	Q96PZ4	SNCB			868960				FBX023				096FV3	1	Q9H7Q1			096GP4	1	HK3	09BZR1	NM 016290	I
0	ENSIO0002/4011 ENSESTT00000026249	44	2625	2625	02	91	53	1011	ST0000031868	FNSESTT00000025931	ENST0000310032	ENSESTT00000025934	SESTT0000002593	SESTT0000002	ST00000274797	SESTT000000259	STT000002593	STT00000555	1298564	ENSESTT0000025938	4		000	961		011000002337	77	ST000032377	SESTI00000002
ر د	A3	7 A	A3	A3	A 3	A3	A3	A3	A 3	A3	A3	A.3	A 3	A 3	A 3	Z 4	Z 4	24	C 4	4 A	73 A3	5.14 5.44	77 73	2 4	C K	۲ رد د د			A3

A3	ENST00000261948	NM 012279	S	6430663 1764725
A3		l	5	76430665 17647275
A 3	59		5	176452251 176458816
A 3	95		Ŋ	176494862 176499035
A3	595			176494862 176500300
A3	59		വ	176494947 176500300
A3	œ	FGFR4	ഹ	497522 176505
A3	ENST00000292410	NM 022963	2	7527 176505
A3	0259	I	2	650,0568 17
A 3	59		2	501099 176504
7.5 A3	59		ٔس	76505115 1
A3			ស	6505286 1765072
A3	50		5	76541049 176612
A 3	00000298507	NSD1	2	30.28 1767036
A 3	025		Ŋ	76543093 1765453
A3	59		5	6612187 1766176
A3	596		5	619693 17665471
A3	'n		വ	6673510 17667452
217 Z Z	2		72	6699894 17670299
Z 4	59		IJ	09391 176710
A 3	270	RAB24	S	76709392 17671122
A 3	FNSESTT00000025981		5	6711722 176714
A 3	59		വ	11722 176714
\ \ \ \	303204	PX19 HUMAN	2	176711736 176714888
Z 4	∞	Q96ME3	5	67197
27	, –	MXD3	Ω.	176715151 176719769
23	0	L,MAN2	Ŋ	62
ر د د	FNSFST#0000055E:		5	176765891 176779165
2 6) } } !	RGS14	Ŋ	765973 1767801
A3	ENSESTT00000025990	t	ഹ	176775288 176776866

176780554	176794461	0890	80614	680853	176817481	7684137	176842058	176844638	176849007	4900	7685057	768497	176842058	176844638	7684900	684900	176850575	176844638	176849007	57	176864135	89	176881467	176880013	Ō	176904318	176904318	177031673	177038162
176779454	176792400	176792400	176804912	7680812	176810246	6834	176834669	176834669	176834669	99/	7683466	176834797	7684109	7684109	176841092	7684109	7684109	176842854	91	176842854	768	176854894	9	176865288	768	89	689	7689193	76897
rV		5	5	5	5	5	S	Z	S	ഹ	S	5	ß	ß	ß	Ŋ	2	Ŋ	5	S	S	Ŋ	ī.	5	5	ß	2	Ŋ	Ω
		SLC34A1			F12							GPRK6									NM 030567)))	DBN1	08088	005	4250	ת ת		
	5992	7	00000	28	ST0000025349	00259	009	ST100000718	599	STT0000002559	ENSESTITO000025998	ST00000230673	SESTEDUDUDOS	002000001100000000000000000000000000000	SESII000002600 SESTTO000002600	260	00970	00000000TE	0000 0000	0220))) o	20000	2220	36000	30750	35 occ	810000032000 80000033000	2	ENSESTIONOUNCENTS ENSESTIONOUNCENTS
رد د	A3	77 73	A 3	Z Z	Z Z) K	?	27.2	2 6) (c	7 7	>17 ~ □) (c	ر د د	A S K	ر د د	7 K	ر د د	AS C k	A C K	A C	A 6	ر د د	A 6	Α κ Ο (A F		A3 A3

176897716 177038203 176898295 176904318	6898906 17690431	691	1807 1769	919402 176924	26890 17694379	6926890 1769616	345068 17709406	399291 17700262	999295 17713328	9295	999300 17700320	999308 17713608	1700321	000783 17713634	001245 177136	007252 17715069	023996 17703819	024173 17703819	024246 1770	77024246 17703711	031099 17703711	77031469 17703819	77031684 1	1702 17703711	7042509 1770488	85 1770	7045241 17705044	77045345 177050
	ഹ	ιΩ	വ	വ	Ŋ	2	5	2	ស	5	5	5	5	5	5	S	IJ	Ŋ	S	5	5	വ	5	5	5	2	5	IJ
096091	2363± 09BXB8	Q9BQB3	NM 024872	$\overline{\mathtt{DDX41}}$		NM 019057	I				NM 017510			•			NM 005451	1	Q14250	Q9BXB9	Q96C91		·	Q9BXB8		NM 024872	I	
ENSESTT00000026016	3198	12	ENST00000274826	ENST00000330503	ENSESTT00000026010	ENST00000329540	601	\leftarrow	ENSESTT00000026013	⊣	0000032817	601	S	575	ENSESTT00000035758		ത	ENSESTT0000035801	ENST0000292374	ENST00000331561		58	580	47	С	y C	357	ENSESTT00000035797
A3	A)	A3	A3			A3	A3	A3	A 3	A3	A3	A3	A3	A3	A3	A3	A3	Z Z	A3	A3	A3	A 3	717 73	7. A	\ \ \	2 4	74 73	A3

7045385 1770504: 052393 17705744 060391 17706490: 060392 17707729	77060394 17707266 77065352 17707700 77078577 17709416	12801 1771363 12810 1771367	10813 17715093 51883 17715931	39504 17715996 36961 17717330	967 17732127 572 17728557	31869 177293	77030 1773782	77030 1773	16183 1774248	177511798 177512883 17753283 177536844	77582334 17758957	77589720 17759447	593021 17759453	77596176 17759678	415/ 17/66 0981 17766	77671613 17768915
ប្រហស	വവ	സ ഹ	വവ	សស	បល	ហេ	വറ	ហេ	റഗ	ហេ	വറ	J.	വ	ഹ	വ വ	υΩ
DDX41	NM_019057	NM_017510	B4GALT7	Q9HAI8	NM_173663	C C F E	08.I.E30	Ç	THOC3	Q9H7L9	FROFI				Y341_HUMAN	YE01_HUMAN
ENSESTT00000035799 ENST0000330228 ENSESTT0000035796 ENSESTT0000035761	788 03579 03579	ENSESTT00000035759 ENST00000332598	294 000	0000030285	30310 32461	003	ENST00000329355 ENST00000331417	32808	ENST00000303154 FNSFSTT00000035763	- ← -	04 2576	ENSESTIONO 0000000 04	STT0000003576	ENST00000332649	74605	ENSESTT00000035/6/ ENST00000313376
A3 A3 A3	A3 A3 A3	A3 A3	A3	A3	A3	A3	A3	A3	A3	A3	A3	A3	A3	A3	A3	A3 A3

744 1776882 44 17768917 77 17768917 65 17769457 69 17769449	745109 1777517 745132 1777466 745132 1777513	77745132 17775139 77745132 17775156 77745132 17775156	7745132 17775176 7745132 17775176 7745132 17775176 7745132 17775176	77745440 177751 77746443 177751 77747326 177751 77749103 177770	49186 17777315 49189 17776318 49289 17777217 49225 17777217 50732 17775176 79162 17778886
	ហលស	מט טט		വ വ വ വ വ	
NOLA2 NM 022471				NM_004499	NM_032921
ENSESTT00000035769 ENSESTT00000035768 ENSESTT00000035770 ENSESTT00000274606 ENST00000274606	4 W V V	78 77 77 77 77 77 77 77 77 77 77 77 77 7	STT000000357 STT0000000357 STT000000357	228 258 3578 3578 3579	ST00000308158 SESTT0000003579 SESTT0000003578 SESTT0000003578 SESTT0000003578
A3 A3 A3 A3 A3		\mathbf{m}	A3 A3 A3		A3 A3 A3 A3 A3

1 1 1 1 1 1 1	438/0 1/81541. 4219 17817121	78153016 178159	78153016 17816761	78157479 17816072	78157835 178	78158920 17817121	159118 17816773	78160838 17816763	78252662 17826962	8267657 1782699	78307485 17830912	78307800 17832294	78400555 17842336	78400555 178425	401325 17840691	1784733	78481825 1785070	8483299 1785053	78505697 1785330		78522259 1785355	78535880 1785368	78564407 17857	78601202 17862129	78623365 1786	78653824 17865419	786544	78661813 17866336	78662264 1786994	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
	ى س	വ	ĸ	τυ.	ഹ	Ŋ	L	വ	ĸ	ιΩ	5	ß	ហ	5	ß	S	ហ	2	· LO	3	5	5	ß	S		· ιΩ	י ער) L	ט כ	7
	VALL	FNITO							ZNF354A					ZNE354B		ZNF271	ZNF454		9 ANHA 9	C # NO A	GRM6			ZNF354C)					ADAMT'S2
	ENSESTT00000025813	α	787	7 a c	ENSEST 10000023813	SII0000002391 STT0000002391	700	7 X Z	, ,	7 (787	l	ENOI OCCOUNTED NO		200) } 	ENCTODOOGGE 101		00230	ENSTUDDOUST 9065	ρα	2 5	o d	006200 5175	ENSIOUCOUSTS / J	\cap \sqcup	o o	∞	ENSESTT0000002580/	ENST00000251582
	A3	A3	A V	Λ k	A3	A K	A K	A 4	A 4	ر د د	2 6	ر د د	A F	A3	۲ رد د د	23	CG &	A3	A3	A3	A c	A C	A C	A3	A3	A3	A3	A3	A3	A3

179215692 1792176 79230857 17923135 79235589 17924504 79235655 17926758 79240421 17924202 79243792 17926755 79246533 17925639	9269772 17931394; 9303154 17930785; 9314421 17931499; 9330648 17933317; 9330774 17933317; 93332229 17933317; 9332243 17933317	79334262 1793 79334633 1793 79334633 1793 79334833 1793 79334883 1793 79334883 1793 79334883 1793 79334883 1793 79335007 1793 79335007 1793
CANX	MAML1 NM_024978 LTC4S	MGAT4B
ENSESTT0000035907 ENST0000329156 ENSESTT0000035861 ENSESTT0000035860 ENST0000247461 ENSESTT0000035865 ENSESTT0000035862 ENSESTT0000035863	STICOCOCOSS 30000292599 30000298607 00000292596 STICOCOCOCOSS STICOCOCOCOSS STICOCOCOCOSS	STT00000359 STT000000359 STT000000359 STT000000358 STT000000359 STT000000359 STT000000359 STT000000358
A3 A3 A3 A3 A3 A3	7 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	A3 A3 A3 A3 A3 A3 A3 A3

179794621 179796637 179816486 179828537 179837361 179875263 179837891 179868310 179861517 179867483 179868152 179889985	80065924 18011086 80065968 18008726 80065968 18010118 80112873 18011315)126767 18012814)126768 18012814)139821 18014808)145626 18018620	80162667 18016664 80166890 18018628 80229572 18023042: 80275785 18027672 80327203 18032862	7210 1803 7543 1803 8296 1803 9112 1803 9155 1803 9332 1803 2068 1803 2309 1803
N W W W W W		വവവവ	വവവവവവ	
GEPT2	NM_015455 O8TAJO	SCGB3A1	Q8NHB0 Q8NGV0	MGAT1 Q8NBL8
ENSESTT00000328081 ENSESTT00000035876 ENST00000253778 ENSESTT00000035875 ENSESTT00000035875	564 564 563 9	ENST 00000332323 ENSESTT00000035680 ENST 00000292641 ENSESTT 0000035679	$\alpha \alpha \alpha + \alpha \alpha \alpha$	ENST00000333055 ENSESTT0000035663 ENST00000307826 ENSESTT00000035662 ENSESTT00000035661 ENSESTT00000035664 ENSESTT00000035664
A3 A3 A3 A3	A3 A3 A3	A3 A3 C4	A3 A3 A3 A3	A3 A3 A3 A3 A3 A3

80344545 1803467	0345508 180352	0345511 18034679	0384273 18039722	0384335 18039794	0385559 18038776	0386417 18038	0387577 18039721	0435821 18048756	0435955 18044819	0448211 18048756	0525529 18054302	0582152 18059022	10589782 18059196	0590141 18059818	10592305 18059597	30635802 18063731	30650805 18065192	30661176 18066196	91605 18069	30728586 18073109	30731275 18073681	30734864 18073976	30739916 18074178	30740159 18074177	80760899 18077204	80760917 18077246	80769651 18077247	80770	0773587 18078058
5	വ	2	3	വ	Ŋ	ιΩ	5	Ŋ	S	S	5	ഹ	5	2	Ŋ	ഹ	5	Z.	ις	Ŋ	'n	5	വ	5	2	ß	ις	5	2
					NM 152283	I		NM 024850	l		BTNL3	NM 152547	ŀ	Q8N324					Q8NGV1	ı	6360	1		TRIM7	096010	TRIM41			GNB2L1
356	0035	00003565	003567	SESTT0000003567	ST00000330037	ST000003021	SESTT0000003	ST00000231229	SESTT0000003564	0356	99	70	03	705	0003	28095	, w	2936	32827	SESTT000000	က	00	56				ک ر	ESTT000000356	T00000274821
A3	A3	A3	A3	A 3	A 3	A3	A3	A 3	Z Z	A 3	A3	A 3	7 A	A3	A 3	Z Z	Z A	\ \ \ \ \ \	C A	43.									

180773591 18077 80783187 180783	80791085 18079685	80792443 18079288		793672 18079698	30794077 18079747	30797875 18080089	30797875 1	30.797875 18	30854088 18086473	30866068 18088690	30903950 18090488	30988607 180991	90904 18099162	31008629 1810090	5672489 2686723	5675304 2686725	5740528 2676213	5749569 26762	6756741 2676213	6769173 2681048	6769173 2683909	6772654 268104	6772654 2683909	6839038 2686724	6970970 2697218	7031241 2705105	7031241 2705	031241 2705106
5 2	വ	വ	ស	വ	വ	വ	ស	.ഹ	വ	വ	5	ιΩ	Ŋ	J.	13	13	13	13	13	13	13	13	13	13	. 13	13	13	13
		NM_022907	l		TRIM52						O4F3 HUMAN	I			FLT1-001	FLT1									bA57H24.1-001	C13orf12	bA97E23.1-001	bA97E23.1-002
S L	566				ENST00000327767	565	56	SESTT000003565	SESTT0000003565	56		ဖ	565	\sim	0		ENSESTT00000037419	0374	42	41	74	41	00374	41	30007	ENST00000255315		100
A3 A3	A3	A3	A3	A3	A3	A3	A3	A3	A3	A3	A3	A3	A3	A3	A4	A4	A4	A4	A4	A4	A4	A 4	A4	A4	A4	PΑ	A4	A4

27051047	4	047	033	699	073	110	298	52	111	615	527	107	554	589	269	269	269	323	\sim	587	944	988	988	9	5772	832	1164	3454)286
27031251	31270	32876	44487	72201	72854	72854	73385	73407	85474	94523	94840	.50695	197451	397451	511516	511760	511924	553849	578843	300764	300922	348687	349033	349033	381547	386617	389004	889008	894554
13	13	13	13	13	. 13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
				~:	8	bA97E23.2-001				bA97E23.3-001		bA161P17.1-001	Q8N5E2	0	0-	0	3-00		2-00	. •		Q8N642	bA274A8.2-001		SLC7A1-001	SLC7A1	SLC7A1-002		
FNSFSTT0000037329	3733	73	3734	71	66943	0071	0000037	3734	03733	00071	003733	00072	5289	0001300073	300072	300072	300072	0003733	130	1300073	0003733	00000323380	00130007	003	007	6	1300073	003733	SESTT00000037
K	P 4	A4	A4	A4	A 4	A4 .	A4	A4	A 4	A 4	A4	A.4	A 4	A 4	A4	A 4	A 4	7 Z	777 A 4	7 T Z	A4	A 4	7 T Z	7 V V	F 7.7	777	F (4	r 7	A4

TABLE 3 (Continued)

79677; 95892 95892 96503 01788	2227 2227 2221 1443 12221	123830 129878 332263 332249	2262 8101 2672 7958 0350	28679163 28655933 28679620 28679146 28679181	866887 869203 873623 873623
7907 907 907 964 014	13650 13654 13891 13913	12380 32907 33100	28310043 28479753 28526203 28580177 28580405	35806 3627 3627 3627 8627 8627	866821 866828 868849 871349
13 13 13 13		13 13 13	13 13 13	13 13 13 13	11 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
SLC7A1-003 Q8N169 Q8TE30 Q9P1E1	UBL3-001	bA90M5.2-001 bA90M5.4-001 Q9H523	3.1	NM_032116	bA374F3.2-001 bA374F3.3-001 bA374F3.4-002
က်က်က်	OTTHUMT00013000746 ENST00000241470 ENSESTT00000037443 ENSESTT00000037445	- L 4	OTTHUMT00013000742 OTTHUMT00013000750 OTTHUMT00013000752 OTTHUMT00013000754 ENSESTT00000037442		075 075 076 076
A4 A4 A4 A4 A4 A4	A4 A4 A4 A4	744 744 744 744	A4 A4 A4 A4	А4 А4 А4 А4	A4 A4 A4 A4

87378	873628	74928	874516	374	079	80028	3820	383810	383	383806	383644	383644	383807	398949	383540	383652	398987	883679	8838	883805	891559	891503	892683	900361	903149	03168	900335	Ō	903168
28714620	7298	729	7	28746140	00	8001	8185	831	8319	8333	8332	38336	38336	38344	88344	38346	38347	38347	383534	383544	3911	891378	892580	898983	8989	898992	899005	89900	901484
13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
bA374F3.4-001	bA374F3.4-004	3.4 - 0	4E3.4-00	bA374F3.4-006	bA223E19.1-001	UBE2L3	bA550P23.2-001	HMGB1-004	HMGB1		HMGB1-001	HMGB1-002	HMGB1-003		HMGB1-008	HMGB1-009		HMGB1-006	HMGB1-005	HMGB1-007	bA550P23.3-001	3.4-00	3.5-0	21019.1-00	00580	bA121019.1-001	•		
OTTHUMT00013000760	_	7	~			ENST00000302464	7	77	ENST00000255320	ENSESTT00000037436	0	300077	770	003743	078	078	743	770	077	078	270	OTTHUMT00013000796	079	080	4		743	74	238
A4	A4	A4	A4	A4	A4	A4	A4	A4	A4	A4	A4	A4	A4	A 4	A 4	A4	A4	A4	A4	A 4	A 4	A4	ΔΔ	71. A 4	7 7	D A	7 7	r <	A4

TABLE 3 (Continued)

7	29136562 29136562 29116533	18278	18302	92555	925553	925553	929770	929770	929658	\sim 1	30362	30361	330472	930433	3305	934763	93470	934727	934976	6827	948783	5110	9	95	29520230	95	952	2
	29107645 29107669 29114473	917534	29175343	29202772	\sim	29254696	27832	29278328	37884		33028	3302	33036	930376	930484	930484	930485	ത	934542	93672	947123	\circ	29508750	5		0875	9	
•	13 13	13	13 <	13 \	13	13	13	13	13	13	13	13	13	13	. 13	13	13	13	13	13	13	13	13	13	13	13	13	13
	ALOX5AP-001 ALOX5AP	bA469L23.2-001			bA252M21.1-001		NM 032849	bA252M21.2-001	_			bA252M21.3-001	bA252M21.4-001	1.4-	bA252M21.5-002	1.5-	1523	ı	bA252M21.6-001	bA252M21.7-001	bA173P16.1-001							
		OTTHUMIOULS000807 OFFHIMPOON 3000804	42	4239	0081	FNSF.STT00000042394	87	0	0081	4239	4247	0081	300081	300081	30008	300082	96	7	0082	0082	8000	4244	4243	4247	1227	C / C /	7575	247
	A4 A4	A4 AA	74 74	7.7 A 4	A 4	7. Z	A 4	7 T T	717 D.A.	7 T	F 7 7	7 7	77	F 7	7 T	7 V	7 Z	r V		7 V	777 707	117	# F	T F	7 K	74 F	A4	A4

29520554 29520554 29520554 29520623 29520623	52062 52062 52062 52388 52388)53406)53406)53406)53406	9520 9520 9520 9520 9520	388 388 371 371 131 023
70000	50875 50875 50875 50875 50875		50876 50876 50876 50876	95 95 95 95 95	900 900 945 945 964 041
. 13 13 13	13 13 13 13	13 13 13	13 13 13	13 13 13 13	11 . 12 . 13 . 13 . 13 .
		00 כ אומנרו	bAl/3Pl6.2-004 bAl73Pl6.2-001 bAl73Pl6.2-002 bAl73Pl6.2-003	· ·	HSPH1 HSPH1
24 40 40 43	ENSESTT00000042443 ENSESTT0000042444 ENSESTT0000042445 ENSESTT0000042402	444	m m m		ENSESTTUDOU0004244/ ENSESTT00000042415 ENSESTT0000042417 ENST00000239887 ENST00000320027 ENSESTT0000042439 ENSESTT0000042424
A4 A4 A4 A4	84 84 84 84	n	A4 A4 A4 A4	A4 A4 A4 A4 A4 A4	84 84 84 84 84 84

206; 388 023	5223	52388	51131	5202	52023	352055	352062	352232	952388	95238	35	35	952062	952	952388	$\boldsymbol{\omega}$	953406	953448	963316	970440	965689	965689	967637	89	017	0175	
29510418 29510418 29510574	51057	51057	51067	51091	510-91	510	51091	51091	51091	121091	151592	95159	951592	951592	95159	952009	952764	95276	957211	957211	963253	29632544	967535	29683426	30111674	011167	02
13 13	13	<u>۳</u>	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
			bA173P16.2-005													,				bA367C11.1-001		bA367C11.1-002	Q9P1E1	bA367C11.2-001	LGR8 HUMAN	bA432E15.1-001	
ENSESTT00000042448 ENSESTT0000042419 ENSESTT00000042425		42	$^{\circ}$		242	241	244	43	42	ENSESTT00000042430	マ	41		43	43	43	40	39	\sim	84	39	084	0319	OTTHIMT00013000846	8386	OTTHIMT00013000848	003745
A4 A4	A4	A 4	A4	A4	A4	A4	A4	A4	A4	A4	A 4	A4	A4	A4	A4	7 7 V	A4	A 4	A4	A4	A 4	7 T	7 A	₽ Ø	7 T	777	A4

1972 30324856 532 30325609 717 30325498	51 3040377 37 3066879	57 3045106	041075	2 3041075	3 304741	1 3048960	1 3052954	054334	055103	7 3066759	413 30668738	7 3060988	1676 30650976	2 30637	5 30634	908 0	12 30650	12 30650	512 3066184	512 3066188	526 3066177	981 30	988 30	6374 30668767	291 3067084	85
3 30218 ³ 303246 303247	30397	30403	30403	30403	3040	3043	30457	30533	30545	30574	30603	3060	3062	3062		3062	3062	30626	30626	30626	30634	30659	3 30659	3066	3 30670	3 30680
	1 T -	13	13	13	13		13	13	13	13	13	13	,1	13	13	13	13	13	13	13	, ,	•			∺	, - 1
Em:AC002525.1-	bA207N4.2-001	DA3/E23.1-001	bA37E23.1-002		Q9H551	[-7]	£66660			NM 023037	İ		bA37E23.1-005		ı						DA37E23.1-006		bA37E23.1-004		bA37E23.5-001	•
ENSESTT00000037458 OTTHUMT00013000850	2 085 005	σ	OTTHUMT00013000855	003746	ENST00000318671	OTTHUMT00013000856	_	ENSESTT00000037461	~	Ŋ	m	744	08	74	74	745	74	74	74	74	085		7 2 C	745	800	980
A4 A4	A4 A4	A4 24	A4	A4	A4	A4	A4	A4	7 A	7 V	77	7 V	A4	7 T Z		. V	7 T	7 T	A4	7 T 7	r (r <	† ?	# F	# K	A4

306982 077180 069872 077090 075222	704 582)27	884 015	32	946)21)15	014	937	\sim	ω	015	α	081	30818554	30910936	\vdash	509	30890057	30870629
30687607 0687617 0687640 0688598 0735410	77	713	30773954 30773954	534 983	976	281	316	290	392)59	195	542	554	08046	30804924	30815994	08161	0849	085273	30864436
13 13 13 13	1 1 T T	13 13	13	13	13	13	13	13	13	13	13	13	73	13	13	13	13	13	. 13	13
BRCA2-001 BRCA2	BRCA2-002 bA37E23.3-001	3.2-00	3.2-0		NM_052818	Q8WTU5	.2-0	bA298P3.2-007	01408	98P3.2-0	ω.		bA298P3.3-001		NM 033111	ŧ	DA11K16.4-001	bA11K16.1-001	bA11K16.2-001	bA11K16.3-001
00374 00367 03746 071	374 036 008	87	800	ENSESTT00000037479 ENSESTT00000037481)	ENST00000306588	87	OTTHUMT00013000878	ENST00000332066	OTTHUMT00013000877		4	OTTHUMT00013000888	ENSESTT00000037478	ENST00000267052	ENSESTT00000037476	9	089	OTTHUMT00013000892	680
A4 A4 A4 A4	А4 А4	A4 A4	A4 A4	A4 A4	A4	A4	A4	A4	A4	A4	A4	A4	A4	A4	A4	A4	A4	A4	A4	A4

A4 A4	ENST0000267068 OTTHUMT00013000897	NM_014887 bA11K16.4-002	13 13	3088903 088903	309109
A4	ENSESTT00000037473		13	8950	40
A4	37		13	950	09083
A 4	03		13	30889684	377
7 7 A	0089	bA11K16.4-003	13	30889998	00806
77. 74	(1)		13	30899013	9081
77. 74.			13	09071	30908872
71. A 4	ENSESTT00000037477		13	30808368	109
2 A A	, , ,		13	30908503	9
77.7 A 4	$^{\circ}$	bA11K16.4-004	13	\sim	30910962
7 T Z			13	\circ	\sim
77) (*.		13	09	
F C	\sim	49J10.1-006	13	30958624	31118238
F Q	787	APRIN	13	30958642	31145465
7 T	· C	49J10.1-007	13	30958685	11823
F17	OTTINITION 3000000	49J10.1-008	13	30958688	Ξ
	FNSESTTONO 0037469		13	30958704	31021469
7 4	OFFHINFOOOT 3000904	49J10.1-002	13	30958706	31022754
T	FNSESTED 000037369		13	31071946	27
r <	FNSESTT0000037370		13	\sim	111327
# F	OTTHIMT000130005	49J10.1-004	13	31073219	107917
r V K	FNSESTTO000037371		13	732	107917
†	OHERTMENON 3000915		13	31125470	31148043
7 V	OTTION TO THE CONTRACTOR OF TH	1-00	13	31125470	31150157
r <	FNSFSTTOUT 3737		13	31130670	31143217
7 Y		100-C-1001		31249569	31283788
A4		PA218218 1-001	13	132	31326539
A4	OJ.THOMI OCCIONOS	100 1 0 TT 10 T 10 T 10 T 10 T 10 T 10		13855	138
A4	ENSESTIOOCOOS/388	KL-002	13	138	31436440
H4	2				

31438279	143828	157814	14789	148403	31558159	148403	31485330	149579	49580	155821	157816	172265	153975	153976	1657	153654	153654	165772	9	165787	534	165347	17	70740	170741	172	72274	204890	31896459
31388571	S	31475278	147682	147700	147773	48200	31483921	49471	49471	501	50222	50235	51056	.510	152757	5	153072	15471	156	91	164969	1649	170581	170598	31705983	172074	_	31727343	31883467
13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
	KL-001	bA81F11.1-001			STARD13		DA81F11.1-005	1F1		bA81F11.1-003			bA81F11.1-004		bA81F11.1-002	H			bA81F11.3-001		bA363P13.1-001			DA141M1.1-001		DA141M1.4-001		DA141M1.3-001	.3-0
ENST0000055481 KT,	13003	300092	7	738)) (ENSESTT0000037387	300093	0092	003737	00	003737	003737	0092	003738	0092	1300092	3738	3738		03738	0093	3737	3738	0094	003738	0000	757500	70000	300094
ΔA	74 A4	777 D.A.	7 T	777	,	7 T	777 74	DA	7 T Z	D.A.	7 7 7 D A	777	7 T Z	F 1 7	. V	7 V V	7 T T	י ע ע	r 6	7 4	7 7 V	PΩ	F17	r	, k	T K	# K	T F	A4 A4

31883467 318964 1983104 3198365 2026796 3204886	2029573 3203206 2190203 3220963	32190245 32209644 32190245 32338382	2190245 3233869	2190316 3220843	2454566 3245544	32807587 33012822	200/30/ 2007983 3290648	2905583 3290648	2946341 3294680	3314456 3404487	1958 340431	9421 101400	9421 1014853	1 1014	9473 10148736	1019492 10148656	21063 1014533	08210	10123176	101273798 101400637	798 10148539	8 1014	101362019 101397352	
13 13 13	133	13 13	13	13	13	F 7	7 F	-1 F	7 F	13	13	7	7	7	7	7	7	7	7	7	7	7	7	
-00 3-0	bA179A7.2-001 RFC3-001			RFC3	bA218I21.1-001	DA266E6.1-001	COO-1 2022C47	DAZ 0050.1.	NA266E6 2-001	NBEA-001	NBEA				CUTL1	CUTL1	CUTL1							mbhmh_gw729093.
700	OTTHUMT00013000954 OTTHUMT00013000952	$\infty \propto$	980	ENST00000255484	30008	0	∞		ENSEST'TOUOUUSABUB		0336	ENSESTT0000038767	7	. [OTTHUMT00007006261	∞	ENST00000292535	0.38	387	. 6	. [FNSEST#00000118	SESTION0000387	664
A4 A4 A4	A4 A4	A4	A4	A4	A4	A4	A4	A4	A4 * 4	17 K	7 7	7 7 7	11 ላ የ	ር 6 7	7.4 A.5	7. A.5	7.5 7.5	7 7 7	A 5	ς κ Ω ιτ	ָ טע	ξ κ Ο 14	4 4 5 4	A5

1 10140534	1400655 10140498	101429721 101452503 101468176 101468461	01477627 10148434	01477627 10148539	1477627 10148743	0148	#C7#CTO# #CC00#TO		TCCC2101	01498891 10152 01101 16886710	277571 970709	101517823 1015	527852 10153012	37904 1015477	547738 10155395	548723 10155550	51346 1015540	1564512 10157683	564512 10158154	0158154	564796 10158630	66265 10157683	566265 1015	576257 10157679	1581374 10158364	101597276 101627593
. 7	7	.2 7	7	7	7	<u>ر</u> ر	-		ŧ	- 1	_	7														
	RG313A17	.fgenesh2						48510	ء ^ا				7	7	.a 7	7	7	7	7	7	7	7	7	7	7	7
.3.86-	=	193468						mbax h 1000485		470211	NM_020979		Hs 7 c1560		mbhmh ts.101.008	1			-		Hs 7 c1564	1			Hs 7 c1565	KRIP1
100322718.100376677	ENSESTT00000038778 OTTHUMT00007007070	C	OTTHUMT0000/00//9/ ENSESTT00000038775	SESTT000003877	_	37	8	OTTHUMT00007006892			ENST00000306803	87	078		0	2.5	ENST00000332533	387	ENSESTT00000038781	87	78	87	87	36	•	
	A5 A5	l i	A5 A5	A5	A5	A5	A5	A5			A5	A5	A 5	A 5	27	ζ K	2 Z	A.5	A5	Z Z	7. Z	21 A	\ \ \ \	ξ Δ	ל ע ת	A5

1	$\frac{6}{2}$	101649629	9677		04/90	66575	166577	101665789	20062	010/39 010/010	01673	016695	576	0167576	01110	0167	01679	98	0167977	0167977	0187260	101681562	88428	101887718	8994	101718623		7	798T/T0	101889940
	015973	101634483	0163/51	100101	0163/12	0165715	101657178	101658436		66238.	0166584	0166586	670	020	8	4	101674370	0167437	456	101675112	101675384	101680646	101684052	101684387	101684414	101684505		i	0168450	101685947
	7	7	- 1	- (7	7	7	_		7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	1958		1.6e7	
		C7orf19	CBCLF2			FLJ20013	NM 017621	1	700_		_NM 152892	l					POLR2J		POLR2J			HSPC047.1				686900 WN	90	5911	.100642795.	
	00	2563	OTTHUMT0000 / 006331	ENSESTT00000038/8/	ENSESTT00000038788	OTTHUMT00007006536		00	OTTHUMT00007006660		ENST00000292616	SESTIOOOO	ENSESTT0000038790	000387	000388	0888000	0700686	888000		0	<u>ا</u>	0700664	0003881	0003881	003881	306682	OTTHUMT00007006603		•	ENSESTT00000038814
	A5	A5	A5 -	A5	A5	A5	A5	A5	A5		A5	A.5	A.5	A 5	. A	ا ا ا	21.5 A 5	7 A	1 4 7	5 d	1 4 7	2 K	ς α 7	ر د د	ט ע ל ג	A 5	A5			A5

01685981 1017934	101691969 101794030	4343 10179478	101694383 101794951	101694776 101695508	01697050 10170	101697479 101707749	01697813 10180137	101710309 101817727	01713854 1018133	01724207 1018	101739241 101839744	01739246 10186671	01739290 101	101739330 101744501	872	452 10177358	101755410 101861246		01757047 10176316	101763162 101768147	186998	1768689 10177356	68862 10177353	101774402 101780795	01783624 1018845	01783749 10188455	01783754 10181767	101783754 101817670	101793580 101890696
	7	7	7	7	7	7	7	7	7	7	7	7		7	7	POLR2J2 7	7	mbhmh_H_RG158017	F218045.fgenesh2.3 7			<i>L</i> .	NM 145325 7	.2	7	7	RSG5 HUMAN 7	CAPRI 7	7
ENSESTT00000038819	FNSFSTT00000038831	003879	003879	003879	003882	00388	03882	003	003882	003882	003881	00	SESTT00000038	ST00000297278	SESTT0000003	JMT000070071	19405	THUMT0000700		OTTHUMT00007008004	00003879	SESTTOOOC	346		003881	388	52940	7	003879
A5	A.5	A 5	A.5	A 5	A 5	A 5	A.5	A.5	A.5	A5	A5	A5	A5	Z Z	A.5	A5	A5	A5		A.5	A5	A5	A 5	4 5	7. A	. □	7 A	2 4	A5

و					- c	> (γ) ι	_ ,	₩	€ #	, 1	ഗ			Н	7	œ	<u>ი</u>	\leftarrow				0	7	7	က	က	13	ω ,
2303	228534	4004	40%2		4 T	4007	7.73	7.7	270	28829	9994	966	2995	299531	2995	3212	3295	3163	320			33143	321	342	34	353	235332	239645	238651
0	1022	\vee \circ	707	V C	V	70	102	102	102	102		102	102	102	102	102	102	3 102	10			7 102	8 102	0 102	4 102	3 102	3 102	0 102	8 102
121	432	シ な 4	2000	3.70 2.70 2.70 2.70	- (042	453	517)25	76116	76116	76139	276251	276251	76251	0350	03502	04193	0433			30196	316038	\sim	50	304	35304	37612	\sim 1
0	10201	77	-1 т	021 021	200	\sim	21	1022	10227(10227	1022	10227613	1022	1022	1022	1023	1023	1023	02			1023	1023	1023	1023	102	102	102	102
																٠													
7	7	<u> </u>	<u> </u>	. – 1	- 1		7	7	7	7	7	7	7	7	7	7	7	7	,			7	7	7		7		7	7
									m											828	0								
NM_1-45032	0	,		~			<u>5</u> 8		c1593	ı		195	31905	21	. 22	ļ				10081562	2 E C		1	V.			7	-	
NM_£	Q8N1F		LRRC17	P37NB			800980		Hs 7	! !		MGC3195	NM 0319	08IZC1	081ZC2	1 1 3				ر د	101274767	19823891	' ! !	7150)		71597) 	
																				աեհա	101	198,	; ; 	Пс 7	١		7 27	1	
		69		60	.75	170		74	36	9/(75	104	! !			171	170	- [170	717	176			700	\circ		000	00 5	164
13221	3196	00400	49377	07006209	00040175	0040070	5370	0004017	07007936	0004007	00400	07006404	3716	0470	22420	0004017	000401		0004017	04000	900/0		C	92054	0/00/	17777		7,000,00	000401
\sim	00031	00001	30024	r0000	10000	r0000	00033	r0000	T0000	T0000	T0000	00001	00000										C					ノ 、	\supset
ENST00000	ENST00000313196	SEST	ENST0000024	LTHUM	ENSESTT0000	NSEST	STOO	ENSESTT0000	TTHUM	ENSESTT000	FNSESTTOOO	TTHIIM	NOTON	FNCTOOOOGO			ENSEST 1000	NOEOL	ENSESTTOOO	NUTRO	OT"THUMT.OUU		00000	ENSTROOO	OTTHUMTOO	ENSTOOOOS			ENSESTTOO ENSESTTOO
r.																												_	A5 E
A	A5	A5	A5	A5	A5	A5	A5	A5	A	A S	717	4	17 6	ζ κ	Ľ F	ť r	ď F	ď i	Ä	ď	Ø		,	∢ ,	¥ f	₹ 1	€ :	A	A; A

102411289	0248113	102399966	41136	46328	102463286	12	102481130	102511457	102513390	5132	51145	1373	5456	102520658	5208	102528369	102528679	102528679	54574	10254574	10254574		102545791	102545791	10251	102517068	1025456	10252306	
102376238	3763	102398168	39905	246297	2462	102478355	102478580	102498413	102498424	102498438	102504818	102513072	102513452	51345	51345	51	102513455	,—;	S	51345	102513455	102513455	102513455	102513455	102513480	0	0251350	0251350	1007070
7	7	, ,	,		7	7	7	7	7		7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	- 1-	- 1-	•
	969	NM_182634		S100A11P	S100A14		08N7T0	t	PMPCB	PMPCB			mpp11	4 4										,			ţ	ZKEI	QSBVAL
1910000000mmoaoma			\circ	ENSESTTOUCOUGAGLOU	70	004015	0297		700622	2692	FNSESTF0000040083	FINSESTTONO 000005	OFFHIMTOROGOGG 10022	FINSTSHIPOODO 1 20 ENSTEADOUNDO 1 4 9	004014	SII000003013	004044	יו ע	004013	0004013	SESTIONOUN4013	0004013	0101000	0004012	7101000	SESTIONOUGHOLD	004	927	ENST00000222539
LI F	A5 A5	A5	A5	A5 A5	74 6	2 Z 2 Z	Ω Ω	ر ا الا) L	2 Z	2 K	ζ K	ζ K	ζ κ Δ	η γ Ο υ	A to	A 4	A F	A B	η κ Ο μ	ָרָ וּ	ζ F	Α, κ Ο Π	A t	A C	A5	A5	A5	A5

2516740 1025208	98	7 102517478 102528679	7 102517478 102528679	7 102517478 102545745	517478 10254574	7478 102	102517478 10254574	7478 10254	102517478 10254579	102548636 10256374	102548652 1025697	102548654 10256979	102548658 10256918	548673 10256528	102548673 1025697	102548684 10256528	0 10256903	c1604 7 102549579 1025497	7 102556671 10256528	56671 10256528	556671 10256979	102562512 10256528	7 102562512 102569791	101446068	E	575377 10260063	HUMAN 7 102575377 1026224	7 102672768 10319049	٢
ENSESTT00000040148	04014	04014	04014	04013	0401	0401	04014	00401	004013	0400	ENSESTTO000040097	0400	70061	00401				OTTHINT00070711	004010	FNSESTTONO0040104	FNSESTT0000040102			700708		2		100	00000
ል ጊ	7 A) H	C 4 6	C 4 F	A3 F	AD F	A C R	ל ג ע	ر بر بر بر	C K	ς α 7	ζ κ Σ	γ γ Σ	2 d 2 d	7 K	ζ K	ת ה	ر د د	ر ا ا	ζ κ Σ	Z K	ر ر بر د	ት ሉ ር ር	ΣΑ Δ.			L.	A L	Ab

102694757 102690743	2004/3/ 102692014 601660 102698900	10271637	21238	102743823 102746233	795307	102828853 102831012	102836540 102853738	98905 10292416	34831 10313653	103135443 103135619	103327319 103337875	103327321 103408971	327826 103408	103368963 103389283	103380669 103381272			529801 10371475	103529849 104107212	103868727 103869859	3868727 10387055	103868774 103870161	103871565 103871676			387281 10393819	103939577 103945127	997484 1040	104027314 104027771
٦	` [7	7	7	7	7	7	7	7	7	7	7	7	7			7	7	7	7	7	7			7	7	7	7
									PRO1598	NM 018503	1	ORC5L	ORC5L		Hs 7 c1615	<u>_</u>	1031 <u>4</u> 6066 m	21002648 2	!		Hs 7 C1617	1	Hs 7 c3016	mbhmh h 102246067	103146 <u>0</u> 66 m	100		nh nm qi16307605	Hs_7_c1619
•	00401	ENSESTT00000040124	04012	01010	0401	FNSFSFF000000118	ENSESTION OF TOTAL	ENSESTION 0000 1011 4		.952			ENST-0000097431	ENGESTTO000070875	0774				5780700000mm3d5Nd	~ O	CHITTENST 000000000000000000000000000000000000	OIIHOMIOOOO1001034		OTTHINTO 007047	•		ENSESEMPOOOO00873	CHARLING COCCO COCCO	OTTHUMT0000705559
	A5	A5	ر د د	C 4	A D D	7.1	ζ k	ζ Κ 7	ζ α 7	2 4	. Z	2 4 7	7. Z	ς κ υ	ל ול ה	A 5	?		K	A F	Α. Ε. Ε. Ε.	AU F	Λ K	ς κ Σ	3		K	A E	A5 A5

_
ਰ
짱
3
=
Œ.
Shirt
ت
=
$\stackrel{\boldsymbol{\sim}}{\epsilon}$
=
<u>ر</u>
Э Ш
Э Ш
Э Ш
) Е

104142399 1041633. 04191028 10419118 04215182 10424204 04215182 10426325 04215182 10426500 04215182 10426500 04215182 10427575	04215186 1043143 04215192 1042420 04215192 1042632 04215192 1042757	4184 4193 4193 6432 6432	04284368 10428118 04267501 10427573 04278279 10429110 04279822 10429033 04302560 10430757	04307682 10 04307682 10 04308132 10 04308136 10
			-	
Hs_7_c1620	MLL5	MLL5 095038 Q8IWR5	Q9NS29 Q86W16 Q86W12	Hs_7_c1623
ENSESTT0000041852 OTTHUMT00007007780 ENSESTT00000041867 ENSESTT00000041864 ENSESTT00000041865 ENSESTT00000041865 ENSESTT00000041862	ENST00000311117 ENSESTT00000041854 ENSESTT00000041853 ENSESTT00000041868 ENSESTT00000041855	0700651 57745 33597 0004185	ENST00000222422 ENSESTT0000041858 ENSESTT0000041859 ENST00000334914 ENSESTT0000041860 ENSESTT0000041861	400000
A5 A5 A5 A5 A5 A5	A5 A5 A5 A5	A5 A5 A5 A5	A55 A55 A55 A55	A5 A5 A5 A5 A5

104308939 104313681 104310018 104311845 104311672 104318457	104312977 104314348 104317346 104469993	04317350 10447	1 10447001	8968	18221 10458970	18221 10458983	0440463	04318558 10447001	04318558 10458968	04318558 1045897	8 10458983	4 10447001	04346254 10458968	46254 10458970	346254 1045898	7001	61279 10458968	279 10458970	04361279 10458983	0180 10439080	104405611 104405835	45633 10444594	4502500 10450306	55221 10455	104657493 104709424	104658206 104660239
T	r r	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	<i>L</i> .	7	7	7
Q86TI3	Q86WG0 SRPK2	SRPK2																		Hs 7 c1625	62	7	$^{-7}$ c1	9	M_019042	I
ENSESTT00000041873 ENST00000334884 ENSESTT00000041909	ENST00000334877	ENST00000257701	ENSESTT0000004	ENSESTT0000004	ENSESTT00000041			ENSESTT00000041		ENSESTT0000004		ENSESTT0000004190	ENSESTT00000041		ENSESTT000000418	ENSESTT00000419	ENSESTT000004190	ENSESTT00000041	ENSESTT0000004	OTTHIMT0000700778	OTTHUMT000070077	OTTHIMT00070070	CT00000TMINTO	67707000TMIHTTO	ENST00000257687	ENSESTIO00000
A5 A5 A5	A5	A5	A5	A5	A5	A5	A5	A5	A5	A5	A5	A5	A5	A5	A5	A.5	A5	A5	A5	Δ 5	A 55	2 A	2. \ 2. \ 7. \	2 K	ζ \ 2 \	A5

7 104658241 10470700 104658637 104723197 104683290 104723218 104706926 104723218	7 104733157 104743633 7 104733157 104764927 7 104733157 104766577		7 104751134 104768660 7 104766086 104770452 7 104766102 104770414	104766102 1047704 104766110 1047702 104768394 1047824	104768394 10478266 104768432 10478243 104783163 10478406	7 104783236 104784089 7 104783236 104784134	104792239 10484402	7 104808623 104811530 7 104808830 105077559 7 104814454 104825244 7 104815496 104893101
FLJ20485		NM_021930	FLJ11785			7	Hs_/_c1634 mbhmh_h_103713457 _104613456_m _26903715_2	YC18_HUMAN Q9BTQ8
ENSESTT0000041892 OTTHUMT00007006894 ENSESTT0000041890 ENSESTT0000041891 ENST0000320648		257700 00004187	OTTHUMT00007006406 ENSESTT0000041887	ENSESTIO0000041886 ENSESTIO0000041889	70004188 327788 310149	329090 332220	OTTHUMT00007007834 OTTHUMT00007006590	ENSESTT0000041883 ENST00000297416 ENST00000275664 ENSESTT0000041880
A5 A5 A5 A5 A5	A5 A5	A5	A5 A5 A5	A A S	A5 A5 A5	A5 A5	A5 A5	A5 A5 A5 A5

104818847 104893101 104821070 104893101 104961923 105077563 104962355 105077535	04989335 104993 05020472 105021 05020547 105021 05076067 105077	105076766 105083558 105095260 105151278	3 10522381 1 10519731	105202525 105205801 105205474 105231797 105205482 105221463	38 1052324 34 1052347	5291482 1053135 5291489 1053135	105292251 105294130 105292251 105298877 105292251 105313289 105292673 105300262
		,				L	
		7 57 7	.0 .2.1 7 7	7	713457 690371 7 7	7	
	1	371345 m 2	bhmh H DJ0568B10 F020305.fgenesh2		_103 _m_2		
M_152749 bhmh_nh_h 103713457	c1637	Hs_7_c1638 mbhmh_h_1037134 _104613456_m _26103716_2	1 H DJ 305.f	52750	bhmh nh h 104613456		
NM_152749 mbhmh_nh_ 10371345_ 10461345		Hs_7 mbhmh 1046 _2610	mbhmh_H F02030	NM_152750	mbhmh1046	SYPL	
000041881 00041882 00041879 18724 07007007	2)7841)6283	07006180	\sim	007006497	06260	000035754 000035753 000035750 000035752
000004188 000004188 000004187 0318724 000700700		000700784					
ENSESTTOOO ENSESTTOOO ENSESTTOOO ENSTOOOOO3	OTTHUMT000070078 ENST00000329846 ENSESTT00000357	OTTHUMT000 OTTHUMT000	OTTHUMT000 FNSESTT000	ENSESTIOOO ENSTOOOOO3 ENSESTIOOO	OTTHUMT000	OTTHUMT000 ENST000000	ENSESTTOO ENSESTTOO ENSESTTOO ENSESTTOO
	OT. ENS	OT.	TO I				
A5 A5 A5 A5 A5	A5 A5 A5	A5 A5	A5	A5 A5 A5	A5	A5 A5	A5 A5 A5 A5

105300133 105313289	05326309 10532767	05451187 1054858	5451529 10547030	5451529 1054712	5451529 10547602	5451529 1054	451529 1054861	5451529 1054865	5452034 105454	5452060 1054858	5462192 10546447	69472 1054855	473329 10548616		473329 10548658	516202 105516	831822 10583234	83305		833369 1058	5861166	61484 1058	471701 735	471701 7373	472141 73	73581559 73730469	73637423 73730476	73668375 73670920	96492 7399
7	7	7	7	7	7	7	7	7	7	7		7	7	7	7	7	7	7.		7	7	7	10	10	10	10	10	10	10
	Hs_7_c1643	PBEF								PBEF HUMAN	1					Hs 7 c1646	$^{\mathrm{Hs}}$ $^{\mathrm{7}}$ c1647	$\mathrm{Hs}^{-7}\mathrm{c}3104$	$\frac{1}{mbx}$ nh chr ⁷	$105.00\overline{6}$.	NM 175884	Hs^{-7} c1648	1	CBARA1					NM_138357
ENCECPPO 0000035751	0700787	OTTHUMT00007006155		ENSESTT00000035746	ENSESTT00000035745	0003574	000357	ENSESTT00000035738	000357	255	ENSESTT00000035748	003	000357	0003574	000357	0700787	0700787	0700758	0700626		ENST00000315965	007	0002127	11182	0000	7717177	o C	\sim	313314
ار بر	A5	A5	A5	A5	A5	A5	A5	A5	A5	A5	A5	A5	A 55	A5	A.5	A.5	A 5	A5	A 5	?	Z Z	4.15 A.5	2 d	217	2 4	917	ט ע	2 4	A6

73990183 73988744 73992055 73988744	3739 3688 2887	74046965 74058975 74059139	41792 41792 41792 41556	41554 42012 42361 42367	42352 42296 42724 42724	74272456 74272402 74272456 74346541 74340393 74345507
73796537 73797084 73797084 73964348	73997942 73998160 74016118	03494 03986 03997	411258 411258 411258	212 577 148 148	22655 22946 23888 24373	74258724 74260633 74260633 74279052 74332501 74332502
10 10 10 10	10 10	10	100	10 10 10	10 10 10	10 10 10 10 10
Q96FL3	NM_152635 Q8WWZ8	PLA2G13	P4HA1 P4HA1	NUDT13	Q9Y3X2 NUDT13 SGT1_HUMAN	Q9Y2I0
ENST00000286508 ENSESTT00000021273 ENSESTT00000021272 ENSESTT00000021275	00000260885 00000334011 00000334011	SESTT0000002145 SESTT0000002145 ST00000260878	0032368 00263556 00307116 000002152	00000021 00000021 00299408	ST00000335635 ST00000325946 ST00000263565 SESTT000002152	ENSESTT0000021522 ENSESTT0000021524 ENSESTT0000021523 ENST00000242505 ENSESTT0000021459 ENSESTT0000021460
A6 A6 A6 A6 A6	9 4 4 9 4 8 8	A6 A6 A6	А6 А6 А6 А6	A6 A6 A6	A6 A6 A6 A6	A6 A6 A6 A6 A6 A6

				•																								
	435	435701	435510	435871	435871	43798	446311	439776	451841	74505217	451843	451843		448782	451843	51	451843	1843	45184	51843	51843	451843	74518436	74518419	74518436	1843	74537973	74600362
74338355 74339356	477	·W	3	43575	435756	43581	435812	833	447981	74480456	448451	74484518	448451	448583	74487551	448755	48755	74487935	487	74487935	48793	74487935	74487935	74487963	74487976	4927	52891	74541167
10 10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	. 10	10	10
	DNAJC9	MRPS16		-			NM 145170	Q8 <u>N</u> 7D5	ANXA7	ANXA7																	Z,MYND17	PPP3CB
ENSESTT00000021463	000002140	0029941	SESTT0000002	000214	002146	0002152	10715	00008653	7791	. 6	2000	STT000000150	ST1000002150	0002136	0000151	0002150	SESTIONO0002150 SESTTOOOOO02150	0002130	002151	00007151	00002151	ESTICO00002151 FSTT000000151	SESTIONO0002151	353110000002131 3531100000001131	SESI 10000002131	SESTIONOU002151	SESTIONOUNDELST	026592
A6	0 ¥ 0 ₹	94 A6	A 6	7 A	710	A 6	2 Z	217	2 4	212	710 P	ט ע ג ב) (4 (4) (4) () ()	0 V	Q	0 4	AO A	P P	2 4	ט ע ג) (J	9 4	Q F	A P	A P	A b	A6 A6

74575867 74575867 74575867 74571979	460025 457586	74600362 74601061	462167	514	474228	75539	480211	479914	83576	83801	83801	86995	751	85619	87554	487514	487514	4874	488057	74877339	488051	48834	74888015
74542284 4542284 4542546 4542559	45426 45487	457927 460010	460190	463 173	3634	474989	477896	47871	483492	483626	483626	484873	484873	84877	485119	487016	487277	487336	487	74876947	176	74877622	74886411
10 10 10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Q8N3W4		NM_152586	L DOXYA	17071	NM 024875	l								SEC24C				NM 173540	09 <u>6</u> CJ6	ì		
NSE SES SES	320361 320361 00002150	SESTIO000002149	9786	SESTIO000	833 238	ST0000029940	ST0000031038	SESTT00000002	000214	33366	3234	00002	ESTT0000002147	SESTT0000002147	ST00000313749	SESTT0000002	SESTT0000002147	SESTT000000147	ST0000326248		20000	ESTICOCOCCIII FSTTOOOOOO2147	ESTT0000002147
A6 A6 A6	A6 A6	A A 6	Ao A6	A6	A6 7	4 A	A6	A6	A 6	A 6	A6	A 6	9 T	7 A	7 P	7 A	9	217	94) (d	0 ¥	04	Ao A6

7										,	~~	_	~~															
8877	80	7000	9435	9461	0396	896595	85	906153	903751	903751	906153		906153	2	4	4	_	3	2	2	3	5	2	9	m	5	\vdash	\vdash
4 7	3 748	F /	74	74	7 74	4 74	1 74	7 74	2 74	5 74	5 74	3 74	8 74	91309	91614	91630	97894	97744	97882	97882	97888	97893	95171	197883	9788	197893	195265	497889
8864		930	934	938	945	9548	9716	9718	00073	0087	0437	043	0526	7		7	74	74	74	74		74	3 74	3 74	3 74		2 74	7
	748	r 🗸	「マ	4	748	748	748	748	749	749	749	749	749	9	15239	16017	16862	19376	19376	19376	19386	19386	19578	21388	21388	21388	21432	53412
														9	749	749	749	4		749	749	749	749	749	749	749	749	749
	10			10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10		10
3P2	5	ָּדִי ר			87			F3				20		8	89		2G	A4	16	001222								
Q96BP	COMO	ČONDŽ			0949			Q9H8I				Q8N420		NDST2	Q8WV68		CAMK2G	Q8NIA4	NM 172.	NM 0	ļ							
				•																								
	80	ά,		ω		84	85		∞	87	88		89								193	06		195	194	6	9	192
018	00214	o c		021	2558	000214	00214	10153	000214	0000214	00214	1325890	00214	9641	9979	96	2680	5762	63	7853	00214	00214	00214	00214	00214	00	00214	00214
0003	0000	200	000	000	\simeq	000	9	33		0	000001	0032	0000	00029	30	33	000322)03	032	00027	000001	000	000001	r00001	r0000	r0000	r0000	r0000
NST00	SESTT(ひさいている	ENSESTIO(SESTI	ST000	SESTT(SESTI	ENST00000	ENSESTT	ENSESTT0	ENSESTT	ENST00000	SESTI	ST000	ENST00000	STOOD	ENST000(ENST000	ENST0000	ENST000	SESTIO	SEST	ENSESTT(SESTT	SE	SESTT	ENSESTT00	ENSESTT00
	ENSES	i i	Ä	EN	EN	ENS	EN	EN	EN	EN	EN	EN	EN	EN	EN	EN	EN	EN	EN	EN	EN	EN	ES	EN	EN	EN	EN	EN
A6	A6	2 4	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6

19592 9765 1858		26	85	92	9/	85	76	1858	∞	16	H	('')	522	517711	521902	233	520678	521902	522333	522333	522288	22439	525518	525542	2295	75234365
50 01 02	501	501	502	502	501	502	501	02	517	517	16	\sim		744	922	92	052	15	155	18050	911	22927		78	29527	33235
75013538 75013538 75013538	501433	501549	501549	1590	501639	01639	501764	501764	51024	510247	10247	56	7510	51	5	7517	52	\sim	2	7521	5	5	52	52	2	7523
10 10 10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Q8nak4			PLAU								NM 003373	VCL										AP3M1		NM 030970	1
ENSESTT00000021181 ENSESTT00000021180 ENSESTT00000021179	317358	SESTT0000002118	ENSESTT00000021182	424	ENSESTT00000021176	9	SESTT00000021	ENSESTT00000021177	STT0000002118	2	ENSESTT00000021186	ST0000027782	1199	00002	00001	ESTT0000002118	000021	SESTT0000002119	0000211	ESTT0000002119	00000211	SESTT0000002120	ST00000330581	SESTT00000	ST00000323546	SESTT0000
A6 A6 A6	A6	Ao A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A 6	A 6	77 P	A 6	

75632868 75813656 75328956 75812806 75632868 75704867 75704867 75928380 759247950 76076904 76076904 76135407 76076904 76135407 76076904 7613537 76199990 76213537 76213531	625543 623029	76280615 76281496 76322599 76335808
7525568 7525568 75255640 7525640 75280904 75280904 75280904 75280904 75280904 75280904 7593980 75930980 75930982 75930982 75930982 75930982 75930982 75930982 76083627 76198802 76198802	6215997 622897	76254890 76280444 76314523 76314523
10 10 10 10 10 10 10 10 10 10 10	10	10 10 10
ADK MYST4	796967	NM_144660
TT00000021 T00000021 T00000021 T00000022 T00000022 T00000022 T00000022 T00000022 T00000022 T00000022 TT00000022 TT00000022 TT00000022 TT00000022 TT00000022 TT00000022 TT00000022 TT00000022 TT00000002	ENST00000330673 ENSESTT00000021124 ENSESTT00000021138	T00000287258 ESTT0000002112 ESTT0000002112

											٠																				
	763356	633580	633546	633263	6339	76339540		76340289	634031	65060	50577	651178	5121	651181	899	14	716314	38944	6173	77661593	77661714	170	3227	8225	69	8019	00663	08	382	0536	
	763152/	631539 777 # 27	631594	633367	9	76338332	633833	76338434	63400	65025	65041	65054	76507413	65083	6836	51	1403	3870	4287	46379	50758	91	98196	98210	77991627	99165	99240	9243	0918	78014424	
,		10			10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
	VDAC2		VDAC2					NM 144589	I	NM 032772	ì				Q9P1K6		NM 032024	l							KCNMA1						
	m	ENSESTT00000021128	ENST00000304595	00002112	00002113	00002113	00002113	98482	0002	308111	0000	00002113	00000321905	00	80609	0000	77847	00002	00002110	SESTT0000002110	0000210	00002109	STT0000002110	ST00000331566	ST0000018	20000	STT00000110	011200000	SESII0000002118 SESTTOOOOO03114	SESTT0000002117	
	A6	A6	A6	A6	A6	7	A 6	9 7	A 6	94	2 P	7 P	7 Y	A 6	2 7 Z	2 A	91.4	9 4 1 4	2 4	2 4	21 4	94 8	A 6	9 2	Q (4	9 4	2 4	0 4	O (А0 А6	

78049275	8	812342	81439	814397	821292	82878	820577	825446	874204	72301	874184	8741	883849	88862	896126	91015	889848	891015	891015	891015		891231	891669	892389	893523	3523	94626	78946262	895863
78018433	05367	07835	09963	11655	17755	18905	320489	32526	328785	368645	374055	374056	383695	388469	389515	389651	389667	389667	889801	889919	111	891116	891553	892038	892589	892589	92589	89258	94803
10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
															DIG5								•				-		
FNSFST#0000001173	002	00211	STT0000002116	002116	STT0000021	002116	STT00000211	02114	116	02116	SESTT000000211	02116	073	59	51	00211	3TT0000002	02115	02115	0211	ESTT000002115	00211	002115	002115	002115	SESTIONO0005115 SESTIONO0000115	ESTICOCOCCITS	3110000002	0002114
8	2 A	7 A	7 A	7 P	7 P	7 P	A6	A6	A 6	9 A	71.0 D D	710 PA	21 A	. A	94	917 A	947 8	74 74	2 4	7 A	9 K	A 6	91,	ט קר) U	O 4	0 V	A A	A6

790324 913386 909034 908970 912897 914183 914458	15344 14506 14506 15903 19473	945769 938242 943485 940536 980138 017342	8041/109 80395502 80417109 80417213 80458684 80513633 80513633
7903204 9080509 9081350 908656 910445 913815 913815	79138153 79138226 79139712 79139712	935317(937168) 937180) 939820) 980042) 016038	80244114 80348029 80348029 80410611 80451828 80451837 80486687 80486688
10 10 10 10 10 10	10 10 10 10	10 10 10 10 10 10	10 10 10 10 10 10
RPC1_HUMAN	RPS24 09P1E1	1919	RAI17 RAI17 PPIF NM_153367
ENSTO0000318641 ENST00000277783 ENSESTT00000021121 ENSESTT00000021120 ENSESTT00000021112 ENSESTT00000021111 ENSESTT00000021110 ENSESTT00000021110	ENSESTT00000021108 ENST00000260896 ENSESTT00000021114 ENSESTT00000021113	ENSTUDUOUSIL407 ENSESTT00000021115 ENSESTT00000021116 ENSESTT00000021117 ENSESTT00000021119 ENSESTT00000021253 ENSESTT00000021253	ENST00000334512 ENSESTT0000021231 ENST00000277788 ENSESTT0000021232 ENSESTT0000021233 ENSESTT00000225174 ENSESTT0000021234 ENSESTT0000021234 ENSESTT0000021234
А6 А6 А6 А6 А6 А6 А6	A6 A6 A6 A6	A6 A6 A6 A6 A6	A6 A6 A6 A6 A6 A6 A6

80610640 80617473	066384	066475	066475	74	80984138	1847	1847	395	397	81039731	80719667						33	7	ω	80984701	2	98468	103814	81038418	\sim	3673	103961	81101184
80608432	ເດ	80661840	80661841	80661863	80663244	80715314	80716284	80718201	80718531	80718764	80718926	80719112	80719228	80772270	80789921	34	80928323	80936971	80981513	80981785	80981786	80981808	81035257	81035260	\sim	81035780	103887	81093936
10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	SFTPA2					SFTPA1			•						-	Ф9н392			SFTPA2					SFTPA1				
ENSESTT00000021251	SI0000032928 SI0000032878	00000	ENSESTT00000021247	124	ENSESTT00000021245	ENST00000334432	0329	\simeq	ENSESTT00000021237	$\overline{}$	SESTT00	0	SESTT0000002124	0000021	00000212	0241878	ENSESTT00000021249	ENST00000333539	124245	000002	STT00000021	00	00000214	0242455	000000	0000002140	T00000021	ENSESTT00000021404
A6	94.4	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	A6	9 A	94	7 P	9 Y	A 6	A6	A6

811161		117323	123045	125072	12	2507	3898	123045	125072	127424	12752	29543	133214	134735	34745	137341	137343	81373438	145672	151688	151688	151688	168	151	81515572	15	$\overline{\leftarrow}$	1569	
811101	81116552	117302	119066	19074	120227	12263	839	122839	122839	\sim	126879	29442	132	134	81346244	1362	13620	13	81456301	150300	150300	150303	15	150	81506170	5	81515319	81557063	
10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10.	
		C9F19O	`								296ГН							SETED				NM 025125	į						
0000214	002	$\tilde{\mathbf{c}}$	445	000214	02145	002144	45	00214	02144	5740	9818	0002144	14	2535	002	0002144	. <	56035	\sim	9	FNSF.STT0000021408	6052	FNSTSTT0000021409	00000141	SII000002217 STT0000000141	0002221		0002141	
A6	A6	A b	A A	0 4	A 10	A 6	A6	94	A6	A 6	7. P	7 P	7 P	917 120	27	9 4	\ \ \	0 4	2 4	9 4 9 8	9	917	2 4) (d	0 Y) (J	A C	7 P	,

1	1566481 81568	1568379 815	81579472 815820	81579821 8	81579821 8	81579821 815	81579932 8	81580186 815	81583422 8158794	81591229 8162990	81593529 81597	81671552 8167201	69615	81697070 8169747	81697983 8169902	81700853 817136	81700889 8171401	81705012 8171401	81760462 8178108	81762785 8177	10 81762846	81781106 8178	10 81781135 8	10 8	0 81832162 8185	0 8183	0 81832918 8185	0 81838176 818	. m	10 81913567 8
								ANXA11					MATIA							NM 138812			NM 032372	1					NM 03233	1
	ENSESTT00000021414	4 1 2 0 0 0 0	00002141	0000211	000002112	00002142	SESTIONOUND142 SESTENOUND00142	011000656217	0000	00002212	0002144	: : cc	808		00000143	00002113	00002113	00002143	2770000	ה בי נכ	20270	000002143	000002111 0316132		1 -	000001110	3E311000002142	SESTIONOUNG142	SESTIO0000002142	121
	ΑG	217	0 4	ט ע ע ג	0 V	0 4 6) (d) () (2 4) Y	2 4	94) (J	A A	A A	94 F	04 6	A A	Ab	A P	Ab	Ab	A P	A P	A P	AO F	Ap	Ab	Ab A

19451	94623	34/21	4343	1942599	195618	1960275	195971	206	207	170	162	160	160	1646324	169	171	$\overline{}$	171	171	\leftarrow	171671	1753	190464	4800	5168	177332	176301	182206	71822522
81913567	1913567	19135/3	81939416 8	81940535 8	194063	81953930 8	1959343 8	067342 8	2074130 8	1452603 7	1571787 7	1599963 7	1605907 7	5929 7	1654577 7	168989	1709544	1712159	1712178	1712203	1712367	1746587	. 629	. 2	71749050	1762023	1762045	1762045	71762045
10	10	T0	10	10	10	10	10	10	10	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
P5	NM_030927							Q8NB58		Hs 7.c5082	1	Hs 7 c1064	1	Hs 7 c1066	l l					LOC155370		Hs_7_c1068		Hs 7 c1069	1 }	٠			
		m	2	ሻ	2				7	8	3	4		9	2		0	3	4	က	2	7	8	8		Q	-		o
ST00000316064	265450	ENSESTT0000002142	ENSESTT0000002143	ENSESTT0000002142	00002142	00002143	ENST00000329171	313	00002110	00700814	00003997	OTTHUMT0000700733	\sim	\circ	00003997	00003997	ENSESTT0000003997	000039	\circ	00700	ENSESTT0000003990	OTTHUMT0000700733	ENSESTT0000003994	7007000	03239	00000	00000399	00000	0000039
	A6 ENS														A7 ENS							A7 OTT				•			

72120515 72121873	183409	192234	119669	182889	212199	183095	183146	8318	318	318	18332	18373	18373	8373	8318	18318	71833202	71837351	71837371	183737	71832800	71834307	72131287	71837371	71837392	71852114	71849602		
71762045	5205	1762	71773689	71809068	71823101	71823135	71830947	71830947	183094	183094	183094	183094	71830947	71830947	71830954	71830954	71830954	71830954	71830954	71830955	71831040	71831040	71831952	71832127	71836013	71842133	71842201		
7	, _	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	_	7	7	7	7	7		7	7		7	400969	
	POM121	095746		POM121																WBSCR20A.1	NM 148936	14937	1			0861176)))	mfhmh h 7040096	1
8 ,			2		m	4			· го	က	-	ıo	. 6	· rc	, v	9 4	. (, c		· œ			ć.	ņα	· 5		30		
0000039	ENSESTT0000003990 OTTHIMT00007006851	275580	00003991	257622	00003991	00003991	00003993	00003993	00003993	266800000	0000399	6620000	6680000	66800000	66800000	66800000	0000000	66800000	66800000	07007000	0330999	のののの名	00000	00000000000000000000000000000000000000		00000000	0283803	8900200	0000
A7 E					•																							A / K	

71842530 71848805	1848707 7215464	1851502 718549	852127 7185236	52462 7185437	7195 718	7188215	1876851 7187743	1877080 7210710	1880796 7188856	1880796 7188856	1880796 718885	1880796 718885	1881128 71888	381128 718885	1881128 7	881128 7188858	1881128 71888	811	1881144 71888	1881144 718	1881144 7188858	71881144 71888584	881902 71888	71881902 71888584	881902 7	2400 7188	882400 7188858	71882996 71888562
							<i>;</i> -						,															
7	7	7	7	7	7	7	7	7	7	7	7	7	7	1	7	7	7	7	7	7	7	7	7	7	7	7	7	7
71300968_m 133605736_13	1		Q8N4N6	Hs 7 c1076	DKFZP434A0131.3	NM 018991										,												
	ENSESTT00000039940	0000399	ENST00000335315	OTTHUMT00007007357			_	00003991	000039	96660000	00003994	000039	96680000	96680000	00003995	000003995	00000399	966800000	00003995	00000399	96600000	0	966200000	00000399	000003995	966200000	966200000	966800000
	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	74	74	7.7	A7	A7

TABLE 3 (Continued)

72028278	031964	72032675	72032723	72032724	72028278	203196	72032675	72032723	72032724	02827	203272	203	72056376	72062034	206203	20620	72056068	72061921	72062076	72062076	07088	72079722	72106243		1	212725	72129318	72134901	72134920
72017507	01750	72017507	72017507	72017507	72018632	72018632	863	72018632	72018632	02076	824	20295	72046727	72046727	204	204676	04	72046778	72057999	72058029	690	750	72085452			2111	1195	72129323	72129324
7	, ,	7	7	7		7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7			7	7	7	7
																NCF1.1							Hs 7 c5085	mbhmh_h_71200968		133605736 13	1	WBSCR20A.2	WBSCR20A
3101000000EEEEE	00041214	0004121	0004121	0004121	000412	00412	004121	004121	0004121	ENSESTT00000041221	004122	004122	0004122	0004122	000412	0070	000412	30925	0004	000412	90626	004	OTTHUMT00007008151	0070065			ENST00000308082	OT-111MT-0007030	310326
ŗ	A7	A7	A7	A7	A7	A7	, ZA	A7	A7	A7	A7	A7	7 A	A7	A7	A7	A7			Δ7	77	A7							

213	13359	213486	15418	215083	214303	214495	21516	214131	72168994		216899	218472	473	216899	22625	1864	34871	227372	230342	234852	234873	238398	238412	238412	238364	238409	38412	72383988
12993	13039	213084	3863	213905	213943	213943	94	214020	15452		72154529	215639	215639	15779	226	26683	226683	22687	227727	30460	23046	236278	236278		സ	36345		72363476
7	7	7	7	7		7		7	7		7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
			NM 178125	Hs_7 c1089	l 1			Hs 7 c1090	FKBP6	mbhmh_h_71200968 72100967_m	33605	1			FZD9	BAZ1B	BAZ1B						BCL7B	BCL7B				
ENSESTT00000041279	000412	004128	(*)	$^{\circ}$	004127	004127	004127	0700741	52037	0			04123	041	00637	5756	OTTHUMT00007007171	004127	04127	004127	04127	004126	3368	700	0004126	00004126	00412	004126
A7	DA7	A7	A7	A7	A7	A7	A7	A7	A7	A7		A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	Z Z	74	777	7.4	747	74	A7

72383646 72383668	38415	0	40501	40503	4050	40497	45096	245096	4229	245091	45097	45094			25076	72497803	49760	72509869	250985	252458	25	2524	72524583	2	51	24	.72524424
72363528	236372	6096	23960	239685	23968	72403031	2419	Δt.	42079	242285	42	43373			7824	72494272	249428	72508698	250917	251002	1003	003	51005	51007	023	72517339	51982
7 7 7	, <u>,</u>	7	7	7	7	7	7	7	7	7	7	7			7	7	7	7	7	7	,	7	7	7	7	7	7
													896														
		TBL2	TBL2			NM 032988	WBSCR14	WBSCR14	-	WBSCR14			mbhmh h 71200968	57 m	133605736 13			WBSCR18	WBSCR18		WBSCR22	WRSCR22					
000412	ENSESTT00000041265	700675	5621	004	004126	_ \	ENST00000243720	OTTHIMT0000700513	0004125	13375	000	00412	7007			FNST00000324941	0000	00700661	4842	004	55758	, –	00/0000	0000122	0004123	0004123	0004124
A7 A7	A7	7 Z	7 A	A7	A7	A7	Z Z	7.4	74	7 Z	77	7 A	A7	:		۲ <i>د</i>	ζ κ Γ	74	74	74	7.4	ָרָ רְּ	\ F	Ç 6) F	/ A	A7

72854615 72896103	2861793 7288756	12819218 72882174	883099 7	72892119 72895391	910253 729	910253 7294	72919602 72925577	932555 7294782	4 7294782	3000780 730	73000780 73023522	73000783 73016740	730218	00792 730218	\sim	7	00811 7302173	00834 730	7304668	36372 7305625	3036372 7305626	036409 7304704	036413 7305	73036479 73055741	73036487 73056261	730	3056	7305574	1 1 1 1 1 1
7	7 7	7														7	7	7	7	7	7	7	7	7	7	7	7		
COCINOC	015337		÷ .		LIMK1	LIMK1									WBSCR1	WBSCR1	WBSCR1			WBSCR5	WBSCR5								
	ENST 00000320399	0000004	000004124	000004124	1265761	02000	00004124	00004124	000004125	000003602	0000003601	000003602	00003601	000003601	265754	002000	265753	5000000	709600000	368	00000	00000	FNSFSTT00000036029	0000003603	202200000	000000360	0000003603	0000003603	
[A /	7 d	ZA	A7	7 Z Z	74	7 Z	7.7	7 Z	74	A7	727	7.A	77	74	7.7	7 A	7 4	ζ K	D Z	7 A	A7	Δ7	, C	ָרָ רָּ רַ	7.4	7.4	7.7	¢

73055741 73080835 73080829	307620	0807	308081	0808	08083	308081	73080828	73232362	322799	322799	320239	20262	279	22799	323080	342901	342885	3381	336460	336133	36108	42902	42902	35175	358711	35267	73564552
73046885 73057931 73058100	305833	73058332	73058332	05833	73058332	73058533	05856	73115902	73143935	73143974	318300	73183883	20273	320304	321295	\sim	73334508	334600	33505	335871	36097	73373585	73427384	73484123	48	73515362	73515542
r r	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
RFC2 RFC2	!					RFC2		CYLINZ	CYLN2	CYLN2						GTF2IRD1	GTF2IRD1			WBSCR23	Hs 7 c1118	1			GTF2I		
ENSESTT00000036035 ENST0000055077	00003610	00000	ENSESTT00000036106	ENSESTT00000036105	0000	\sim	000	00000	0275634	22	000	9	000	00000	ENSESTT00000036043	00000	$^{\circ}$	00000	0	0000	OTTHUMT00007007275	0000036	00000360	00000	000100	00000361	00000
A7 A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7

73564 35664 35664	58525 58525	358710		358195	358564	358635	358638	358640	35758	358195	58564	358635	358638	358640	35819	358564	358635	358638	m	35819	358502	58	61574	73610049	73615593
35155 51554 51554	55 55	351555	51739 56989	356989	356989	356989	356989	356989	118	357118	357118	357118	357118	357118	357230	35723	357230	357230	73572309	57443	58316	58437	73600398	73600417	73600468
L L L	7	7	Г г	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	\circ	GTF2I																					NCF1.2		NCF1
ENSESTT00000036052 ENSESTT0000036049 ENSESTT00000036050	4924	489	0003605	ENSESTT00000035063	9098000	003606	000360	000	STT000000	9098000	00360	003606	003606	098000	003607	00360	0003607	00003607	00003607	00003607	0980000	70950000	1000000118	000003608	289473
A7 A7	A7	A7	A7	A7	/ K	A7	A7	A7	A7	A7	A7	A7	A7	Z Z	74	7 A	A7	A7	7.4	7.7		ָרָ רְ	Z F	\ \ \ \ \	A/

736157 36157 36157 36799 36635	73679927 73718764 73713295 73713351	373386 373386 372603	939	3770 3740 3844 3850 3883	73901788 73901764 73901764 73901764	73954376 73940594 73977192 73969279
736116 361170 361440 362257 362309	73659841 73706764 73710352	371851 371898 371899	71 72 72 73	373386; 373770; 379114; 379117; 386881	73869229 73882190 73889107 73892480	73920467 73920470 73962893 73966809
	r r r r			rd •	トレレレ	r r r r
NM_032203 mbhmh_H_NH0813J07 _F171046.fgenesh2	DKFZP434A0131.1 NM_018991	7_c112 S2L5	Q16673 Q86WY7	mfhmh_chr7.73.013	WBSCR16	Q86WX4 NM_032203
ENSESTT00000036087 ENSESTT00000036088 ENSESTT0000036089 ENST0000302215 OTTHUMT00007006446	00003610 00700721 308103	OTTHUMT0000/008155 OTTHUMT00007007303 ENST0000318547 ENSESTT0000036090		ENSTOCOCOCOCOCOCOCOCOCOCOCOCOCOCOCOCOCOCOC	ENST00000329959 ENSESTT00000036098 ENSESTT0000036099	00334260 000003609 0312575 000003609
A7 A7 A7 A7 A7	A7 A7 A7	A / A 7 A 7	A7 A7 A7	A7 A7 A7 A7	A7 A7 A7	A) A) A) A)

4	739998.	399988	399984	0279	402911	74030393	799	402911	403039	402799	402911	39	402799	402911	403039	402586	02799	402911		406517	41140	452822	0036	12465	74	440222	22	440222		74417728	
	3984	3990	3	390	01390	401390	401390	0139	401390	74013951	401395	40139	401466	9	401466	40183	01834	40183	01834	403379	1118	411412	411493	11501	74115017	74378046	74386841	003	74412873	74415176	
	7	7	7	7	7	7	7		7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
																٠					Q86WY7	ı		PMS2L5							
	ENST00000297905	8	003609	003787	003786	00378	003787	0378	03787	003787	0378	003787	1003787	000378	003787	03787	003787	0003786	0003788	003786	5657	003	0003786	29909	J	2000	000378	2015000	0000700	0003783	
	A7	A7	Z Z	A7	7 A A	74	A7	A7	74	7 Z	7 Z Z	7 Z Z	11. A7	7 Z	747	7 A A	Z Z	7 Z	77	7 4	74	74	7.7	7 7	7 6	ָרָ רְּ	1 F	ر د د	A 4	A7	

A7 A7	ENST00000317042 OTTHUMT00007006787	Q9P1E6 mbhmh_h_72800966_ 73394042_m	7	74415789	74416214
		$13200573\overline{8}$ $\overline{13}$	7	74418388	74470222
A7	ENST00000311251	l	7	74419694	74479430
A7		Hs 7 c1145	7	74523575	74584324
A7		Q8 <u>6wY</u> 7	7	74524542	74556308
A7		Q86WY7	7	74526082	74528285
A7		PMS2L6	7	74526852	74541042
A7	ENSESTT00000037834		7	74528385	74556252
A7			7.	74529200	74566962
A7	ENST00000311139	PMS2L5	7	74529281	74538934
A7	0		7	74529281	74541015
A7		Hs 7 c5090	7	74529284	74600754
A7		1	7	74538952	74567012
A7	ENST00000251624	PMS2L6	7	45	74569067
A7	ENSESTT00000037835		7	74556408	74584271
A7	ENST00000305928		7	5573	6904
A7	0	Q86WY7	7	74582125	74584327
A7		ı	7	74584427	74743294
A7	0		7	74585242	74594942
A7	0310939		7	74585323	74600345
A7	0		7	74600539	74603386
A7	0		7	74600635	74607984
A7	000070081	Hs 7 c5091	7	74605989	74608444
A7	0	[5	7	74606045	74609003
A7	0	DKEZP434A0131.2	7	74606957	74631908
A7	0		7	74607712	74637304
A7	0		7	74607712	74640405
A7	0		7	74611418	74612259

	,	ł		
ENST00000275590 ENSESTT00000037859	Q8WW08	7	74633749 74634716	74636644 74636774
00700627	mbhmh h 73557902			
	$\frac{74457901}{133948896}$ 13	7	74634728	74636644
ENST00000323819	<u>L</u> 08600	7	74636992	74646977
OTTHUMT00007006661	mfhmh h 73557902_74457901 m			
	$13394889\overline{6}$ $\overline{1}3$	7	74640307	74649026
ENSESTT00000037842	l	7	74640495	74645112
00003784		7	74651721	74653100
	Hs 7 c1152	7	74651740	74657781
ENSESTT00000037844	!	7	5174	74656591
		7	74652026	74657514
	NM 145645	7	74654800	74657968
ENSESTT00000037846		7	74655026	74657893
		7	90	74658035
ENSESTT00000037848		7	74657213	74657787
	POM121	7	74658837	74684082
		7	74659912	74663188
	mbhmh h 73557902 74457901 m			
	1	7	74660168	74684082
ENSESTT00000037857	1	7	74664350	74666568
0000378		7	74666904	74679035
ENSESTT00000037855		7	74682449	_
ENSESTT00000037854		7	74716469	74769374
ENST00000301990		7	473652	₩.
OTTHUMT00007007168	mbhmh ts.74.012.a	7	74738139	74744350
00700	Hs_7_c1157	7	74744346	74752527

7 74749246 74756200	74752342 747692	3806 7476922	76940	7 7484064	7 74779537 74786565	IP1 7 74779582 74980306	7 74788329 74797481	799047 7480472	7 74895820 74980379	1160 7 74980208 7498032	75010931 750136	75011028 7503115	75011100 7501358	75053203 7505512	75053203 7505512	c1163 7 75077073 7507754	84 7 75120355 751303	120355 7513417	120424 7	120432 7	120464 7513010	75120490 7512283	7 75120579 7512999	75156536 7522	75156536 7	75156536 752	5156536 75225	7515656 75206369
ENST00000248606	0301956	0000	0	OTTHUMT00007006447	ENSESTT00000037852	03209	00000	000003785	00000	000700740	0	ENSESTT00000040258	0007	0222	0007		7779000	00	000004018	000004018	000004025	0318622	000004	000004019	000004019	000004019	000004019	000004018
A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	7 Z	747	A7	A7	7.4

752263 522636	2 2	51		0	75225046	75225268	75226369	22636	22677	\sim	522677	523604	75236046	523604	523604	604	523604	525529	528934	28934	52	28939	52893	529568	524241	75246817
751565.	$156 \\ 156$	516452		75176809	75195386	75195386	75195386	19538	19538	75195400	522362	522839	75229120	75229129	S	75229333	522937	523	523	75237744	52		523	523774	523774	75237749
7		7		7	7	7	7	7	7	7	7	7	7	7	7	7	7	7 .	7	7	7	7	7	7	7	7
		c_1	mbhmh_h_73557902_ 74457901_m	33948896	I		•			POR		TMPIT														
0000401	ENSESTT00000040202	00700741	OTTHUMT00007006487		ENSESTT00000040200	0004019		0004019	000401	\sim 1	0004020	000000	0000402	00004025	00004025	00004025	00004025	00004024	0000402	00004024	00004023	00004023	00004024	00004023	0	0
A7 A7	A7	A7	A7		A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	Å7

75255296		528934	52	75289395	528941	\sim	27193	28937	28835	530800	53080	30802	30800	75308009	75313204	3162	34281	75373549	m	5	75390964	75418535	75501454	75506790	50	550	75522894	
75237749	75237749	523774	S		3774		523787	52551	528806	528945	4	528948	528953	530574	75312957	31585	4084	75349841	75354317	75354317	75390863	75415144	75443300	75443300	75443307	75476389	75476473	
7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
					MK-STYX		MSTY HUMAN	I			MDH2	MDH2			Hs_7_c3073	7_c117	7_{c512}	Hs_7_c1174	l I	7 c117	Hs_7_c1176	Hs 7 c1177	l I					mbhmh_h_73557902 74457901_m
ENSESTT00000040249	ENSESTT00000040247	ENSESTT00000040246	ENSESTT00000040241	000	7	00	ENST00000248600	\sim	ENST00000315790		ENST00000315758		ENSESTT00000040205	00040	00700775	0	0700804	OTTHUMT00007007443	ENST00000332057	OTTHUMT00007007445	8	OTTHUMT00007007447	ENSESTT00000040208	ENSESTT00000040207	0000402	000004	ENST00000326382	OTTHUMT00007006504
A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7

TABLE 3 (Continued)

o	\sim	5523140 75	75524053 75528692	75543994 75545679	75544012 75545701	7554570	68205 7560040	5570983 7560021	5570997 7	602536 7560350	630735 7565109	5630735 7565110	5631056 7563896	5631465 756	5666341 7568347	666371 7568346	5670977 7568347	75674328 75683368	703078 7572401	703114 757	703116 7572210	75703123 75724122	75703136 75724190	75703141 75747397	75703143 75747007	703158 75721	75711502 75712557	75711568 75712530	
74 7552724	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7 .	7	7	7	7	7	7	7	7	7	7	7	7	1
7547647			NM 153043	l	HSPB1	HSPB1	YWHAG	YWHAG			SRCRB4D	SRCRB4D		Q96BF5	ZP3A	ZP3								DTX2	DTX2		Hs 7 c1183	! !	
7																													
133948896 13	00004021	ENSESTT00000040212	ENST00000326284	ENSESTT00000040213	OTTHUMT00007006552	ENST00000248553	OTTHUMT00007006186	ENST00000307630	ENSESTT00000040235	\simeq	~ 1	OTTHUMT00007006188	ENSESTT00000040234	ENST00000297799	OTTHUMT00007006555	ENST00000257652	ENSESTT00000040214	00000402	0000040	9	ENSESTT00000040218	ENSESTT00000040219	ENSESTT00000040220	0	ENST00000324432	000	000700747	0329896	1
	A7 .	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	

76245780	76265170	76440006	76295598	76269847	76266386			76300760	76294084	76270744	76273767	76281262	76300803	76299277	76313732	76363754			76352916	76363761	76357619	76357592	76409308	76441197	76441207	76441213			76536234
	76255577	76257204	76260312	76263908	76264978			76266095	76266148	76269559	76271927	76279424	76294463	76297956	76313155	76325407			76330887	76351350	76356805	76356814	76364104	76437484	76437495	76437634			76466089
7	7	7	7	7	7			7	7	7	7	7	7		7	7			7	7	7	7	7	7	7	7			7
			Hs 7 c1202	<u>LXM9</u> 80		11359887	.75188365.75365376	.7.9e-							Hs 7 c1203	! }	mbhmh_h_75248517	O	$\overline{19731738}$ $\overline{198}$			Hs 7 c1204	1	mbax nh qi17389564	FGLZ		mbhmh h 75248517	76148516 m	$\overline{19731738}$
ENSESTT00000037258	ENSESTT00000037261	ഗ	070073	ENST00000285792	\circ	OTTHUMT00007006602			ENSESTT00000037291	000037	ENSESTT00000037294		00003729	ENST00000330572	OTTHUMT00007007330	ENSESTT00000037289	OTTHUMT00007006666			FNSESTT00000037288	0327285	OTTHUMT00007007332	FNSESTT00000037260	OTTHIMT00007006412	1248598	ENSESTT0000037287	OTTHUMT00007006667		
A7	A7	A7	A7	A7	A7	A7			A7	A7	A7	A7	A7	A7	A7	A7	A7			A7	A7	A7	A7	74	A7	A7	A7		

76520191	10260	652398	76536589	57138	76571745	76568852			60209	57174	76567945	64747	76596756			76653274	76657235	76751767	76839272	76881437	76842330	8064	76842330	88143	76881437	688143	689500	8814	76889253
NCE87N37	7007# 01336	650150	76523852	S	76552119	76552120			65527	76552993	76562091		76571643			76611431	76638369	76751393	76778862	76778886	76778907	76778915	76805409	76848601	76848601	6848	4860	736	76875004
٢	` '	- [-	7	7	7	7	517		7	7	7	7	7	517		7	7	7	7	7	7	7	7	7	7	7	7	7	7
CQ6Mc1	QSOMEST OGDSS3	X71.245				Q9Y4L9	mbhmh_nh_h_752485	76148516 m	18931739	l		Q8ND73		hmh_nh_h_75248	76148516 m	$\overline{18931739}$	i	Q9BXE6		PTPN12		PTPN12							
FNSH0000085871	Sο	ENSESTT00000037262		ENSESTT00000037263	ENSESTT00000037284	ENST00000257626	OTTHUMT00007007104			ENSESTT00000037285	ENSESTT00000037286	ENST00000334003	ENSESTT00000037283	OTTHUMT00007007105			ENSESTT00000037282	ENST00000310324	ENSESTT00000037265	OTTHUMT00007006825	ENSESTT00000037266	ENST00000248594	ENSESTT00000037267	ENSESTT00000037269	ENSESTT00000037270	ENSESTT00000037271	0000037	0000037	ENSESTT00000037281
k L	, t. k	A7	A7	A7	A7	A7	A7			A7	A7	A7	A7	A7			A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7	A7

76881437 76880309 76937634 76912750 76937634	697783	~ w	01004	77039701	03979	03994	979		19624	77195265	1174155	117412	11741435	117385	11749471	11751257	11751	11753063	11766750
76878133 76878340 76900557 76910887 76925217	9378	693783	76990885	03508	03508	77035096	03525		38162	7096101	1725645	172564	1725647	1733123	748583	174949	174950	52972	117667090
r r r r r r		7	7		7	7	7		7	7	, -1	\vdash	⊣	Ţ	Н	Н	Н	Н	, - 1
	Q86X48 mbhmh_h_75248517 76148516 m	[18931739]198		DC32	C7orf35			h 752 3516 m	$\overline{18931739198}$	Q8TBW4	MAN1A2	,					017709 MN	1	PNRC2
00003	955 00630	77015000000masasna	00003727	ENSEST100000031431 OTTHUMT00007006265	ENST00000257663	00003144	0003144	OTTHUMT00007006310		ENST00000248550	ENST00000256653	ENSESTT00000003501	ENSESTT00000003500	ENSESTT00000003502	ENSESTT00000003523	ENSESTT00000003503	ENST00000328500	31313	S
A7 A7 A7 A7 A7	A7 A7	7 %	A7	A /	A7	A7	A7	A7		A7	A8	A8	A8	A8	A8	A8	A8	A8	A8

117667118 17759186 1	59572 11781859	17818779 11782368	17822324 11784845	822324 117849	17831482 11784910	17842855 11785381	11785912	342865 1178529	342865 11785570	17842866 11807416	17842868 11785576	11788053	17862486 11787699	17885713 11790518	17917336 11794304	17920750 11792835	17943055 1179629	17943058 11797049	17962945 1179703	17974982 11797616	91 11807418	42261 11874327	11882083	18889344 11889039	889622 11889040	8920227 1190	18921825 11893467
	⊣ ┌┤	ᄅ	Н	H	П	⊣	ᆏ	ᆏ	ᆏ	ᆏ	\vdash	ᆏ	, - 1	\vdash	\vdash	\vdash	₽	Н	, 	₽	ᠬ	ᆏ	Н	\vdash		~	ᆏ
	GDAP2		Q9H141	WDR3		i				Q8NAZ1												Q90N81	TBX15			WARS2	
STT000000	ESTT0000000352 T00000263166	00	11	331	SESTT0000000	SESTT00000003	00351	000351	00351	620	0000	SESTT0000000351	ESTT0000000351	SESTT0000000351	SESTT0000000351	SESTT0000000351	SESTT000000350	000035	000350	0000350	SESTT0000000343	ST00000334368	20715	SESTT000000	0000343	0235521	ESTT0000000
ENSE	ENS		臣	EN	EN	EN	豆	豆	豆	[2]	EN	Ξī	E	EN	[±]	Œ	l [F]	<u> </u>	[I	Į.	<u>*</u>	1 12	1 hr.	1 1] [=] [=	1 1-51

118922024 11903 19015816 11901 19035413 11903	19108318 11910892	3217196 11921981	3217256 11924518	19257783 11927	19257783 11928124	19269568 11928124	19270090 11928284	4149 1194036	19304154 11931127	19304154 11931177	19304167 11930860	19304424 11931162	19304427 11940364	19304427 11940405	19328005 11933482	19356225 11936221	19385611 1193858	19396243 11940405	19396244 11939737	19396322 11940405	19396481 11940364	19456897 1194610	5270 11948583	19494238 11949	9511709 11951240	0896 1196332	9600896 11963322
, H H F	+ ←	П	Н	Н	Н	Н	ᆏ	\leftarrow	\vdash	7	\vdash		Н	Н	\leftarrow	ᆔ	⊣	Н	Н	Н	⊣	⊣	\vdash	ᆏ	г - -l	,	H
							HA02	Q8TDP9				HSD3B2	Q8TDP9	Q8TDP9	- 12	Q9H1M9					HSD3B1	Q9UDK8		700D60	Q96IT2	ı	
ENSESTT0000003432 ENST00000333224	0000330630	352	STT000000352	STT00000003	00000353	000000353	594	03	T000000353	STT0000000	000000353	T0000030318	T0000033370	3201	ST0000025658	028619	ST0000033	00000353	0000	00000353	ST0000023554	ST0000033558	ST0000033100	ST0000033522	ST0000027126	STT000000353	SESTT00000003
A8 A8	A0 A8	A8	A8	A8	A8	A8	A8	A8	A8	A8	A8	A8	A8	A8	A8	8	A8	A8	A8	A8	A 8	8	A8	2 A	2 Z	2 A	A8

								:	
119633206 119633222 119633222 119619075 119633222	196578 196578 196578	11965/8// 119700499 119700465 119692170	1969777 1969787 6039212	03433	36039125 36067456 36123079	612539 612224 612224	612307 612450	36107278 36150464 36154698	615590 615431
119601027 119615847 119615847 119616052 119626114	1963738 1963754 1964889	119653323 119683168 119683421 119683593	196836 196875 595815	59583 59585	601242 604242 604242	60424 60427 60427	604279 609053	0662 4244 4244	61424 61449 61449
~ ~ ~ ~ ~			нн 9	999	ω φ φ	, o o o	000	600	و و و
РНGDН	HMGCS2	08ner6	REG4 ST.C26A8-001	SLC26A8 SLC26A8 SLC26A8	MAPK14-002	MAPK14-001 NM_139014	MAPK14	dJ179N16.3-001 mapk13-005	MAPK13-003
		-							
ENST00000263167 ENSESTT00000003540 ENSESTT00000003541 ENSESTT00000003542	6633 000355 000355	ENSESTT00000003544 ENST00000324032 ENSESTT00000003551 ENSESTT0000003550	56585	29784 10888	ENSESTT00000033005 ENSESTT00000032935	060062 060062 29794	.29/95 110795 1000329	00600625 00600627	ENSESTT00000032938 ENSESTT00000032937 OTTHUMT00006006268
A8 A8 A8 A8 A8				A9 A9	A9 A9	A A 9	A A 9 A 9 A 9	A9	A9 A9

A9	OTTHUMT00006006266	MAPK13-001	૭	49	12
~	ENST00000211287	MAPK13	9	36145117	1546
_	ENSESTT00000032940		9	36145142	\vdash
~	9		9	4514	615
Φ.	0000329		9	36145145	36151536
a)	000032		9	36145202	615
ത	000032		9	36145202	36155902
ത	ENSESTT00000032944		9	36145273	36146034
ത	900900	MAPK13-004	9	36145295	36153839
ത		MAPK13-002	9	36145501	36151147
ത	00900	BRPF3-001	9	1140	36247418
ച	(*)	BRPF3	9	1140	36247421
ത	0000		9	621202	62152
0	000032		9	621590	62
ത	0060062	BRPF3-002	9	2513	36247418
<u>ი</u>	21	Q9NWM1	9	622598	624535
<u>ග</u>	0000		9	622866	623258
o)	ENSESTT00000032948		9	623991	62461
ത	OTTHUMT00006006284	dJ50J22.1-001	9	628511	36310051
<u>ه</u>		PNPLA1	9	0	63
S	900	dJ50J22.5-001	9	631703	744
9		0	, 9	633180	36334066
ص ص	0060062	dJ50J22.2-001	9	36380826	40241
م		dJ50J22.2-002	9	36380826	40241
A9	ENST00000229480	ETV7	9	36380827	36402349
<u>ත</u>	\subseteq		9	36390551	36402400
A9	OTTHUMT00006006292	22	9	640146	64066
റ	ENST00000316266	g	9	640	41516
A9	0	dJ347L7.1-001	, o	641209	645752
A9	ENSESTT00000032949		9	36457399	36458352

A A B B B B B B B B B B B B B B B B B B	0265344 00600629 00003295 00003295 00003295 00600630 229812	C6orf69 dJ108K11.3-001 STK38-001 STK38	• • • • • • • • • • • • • • • • • • •	36457399 36484759 36484759 36499410 36501514 36508524 36508531	36505168 36505775 36499460 36503191 36505772 36562102 36562102 36562102
၅ ၅ ၅	ENSESTT00000032996 ENSESTT0000032955 ENSESTT00000032954		000	668099 660833	50210 61643 61754
9999	00600630 00600630 244437 317631	SFRS3-001 SFRS3-002 SFRS3	ى ى ى ي	36609000 36609023 36611395 36688401	36618064 36616672 36617408 36689903
9 9 9	0600 0601 00003	dJ193M11.1-001 CDKN1A-005	0 0 0	668844 669116 669242	668990 669914 670195
64 64 64 64	OTTHUMT00006012684 ENST0000244741 OTTHUMT00006012685 ENSESTT0000032957	CDKN1A-001 CDKN1A CDKN1A-002	0000	66932 66933 66933 66933	670197. 670196. 670055 670195.
9 6 6	000	CDKN1A-004 CDKN1A-003	9 9 9	36693358 36693403 36693403	669913 669531 669531
A9 A9 A9	0006011 0229824 0310390 0006006	dJ431A14.3-001 Q8TDV1 dJ431A14.4-001	००००	36737227 36737257 36751637 36751682	36743433 36745385 36752338 36752618

36772013	685400	36854633	36772015	36772013	677201	36780337	36772025	36873266	3962	36889629	8962	3.6886506	3918	3113	693815	69381	694117	693861	93820	22	693861	694349	36959306	36979463	697946	36974006	36978833	36978833	36979298
36755407	36755410	36755410	36758313	36760019	36760019	36760019	36760024	36869458	36869458	36869463	36870099	36870254	36886501	69004	36900495	36900495	690049	36900540	36900544	36900558	36909132	6943	36954718	36969064	06969	36969360	36969368	36969383	36977621
9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
dJ431A14.5-002	CPNE5	dJ431A14.5-001		dJ431A14.5-003				PPIL1-002	PPIL1-001	PPIL1			dJ90K10.2-001	dJ90K10.2-004	dJ90K10,2-002	dJ90K10.2-003	C6orf89		dJ90K10.2-005			dJ90K10.3-001	dJ90K10.4-001	PI16	dJ90K10.5-001				dJ90K10.5-002
OTTHUMT00006006311	マ	OTTHUMT00006006310	0	0	\circ	\circ	00032	0			00		OTTHUMT00006006316	OTTHUMT00006006319	0600631			ENSESTT00000032959			ENSESTT00000032961	OTTHUMT00006006326	OTTHUMT00006006328	97048	0090		000329	000	0600633
A9	A9	A9	A9	A9	A9	8	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A 9	A9	A9	A9	A9	8 8	9 A	A9	0 A	0 0	0.4	A9

		000000000000000000000000000000000000000	Ų	77000	0.00
O	OTTHUMT00006006335 OTTHUMT0006006341	dJ90KIU.6-0UZ dJ90KIO.6-008	9	36982 <i>1</i> 7 698277	36991863 37000929
O	000600633	dJ90K10.6-001	9	98277	7000
퍼	00003296		9	698321	699278
144	ENSESTT00000032965		9	36983213	37000795
	ENSESTT00000032966	÷	9	36983310	37000795
,	ENSESTT00000032967		9	36983310	37000795
_	OTTHUMT00006006340	dJ90K10.6-007	9	36983368	37000612
,	ENST00000259958	MTCH1	9	36983368	37000747
_	OTTHUMT00006006337	dJ90K10.6-004	9	36983391	36985547
_	OTTHUMT00006006336	dJ90K10.6-003	9	36983543	36992304
	OTTHUMT00006006338	dJ90K10.6-005	9	36984097	36987385
	ENSESTT00000032968		9	36984669	700079
	OTTHUMT00006006339	dJ90K10.6-006	9	36984687	36987307
	OTTHUMT00006006356	FGD2-001	9	37020277	04292
	ENSESTT00000035539		9	37020289	37026654
	ENSESTT00000035540		9	37020301	37028317
	ENST00000274963	FGD2	9	37020330	316
	ENSESTT00000035541		9	37040439	37042882
	OTTHUMT00006006354	dJ405J24.2-001	9	37059462	37060032
	ENST00000297147	095101	9	37059560	37059820
	00	dJ441G21.1-001	9	10	0649
	ENST00000310055		9	37105943	90
	ENSESTT00000035542		9	37184786	37185779
	ENSESTT00000035543		9	37184786	37.185779
	OTTHUMT00006012708	PIM1-003	9	37184834	37190057
	ENST00000259722	PIM1	. 9	18	37190057
	ENSESTT00000035544		. 9	718	37190059
	OTTHUMT00006012709	PIM1-004	9	37187099	37188878
	ENSESTT00000035545		9	37187103	37190059

				1	0
A9	OTTHUMT00006012706	PIM1-001	9	71871.	ത്
A9	000003554		9	71871	19005
A9	0006012	PIM1-002	9	718762	7190
A9	000	dJ355M6.2-001	9	722681	727278
A9	3168	Q8TC54	9	722681	72336
A9	0900	ó	9	722706	727226
A9	ENST00000316909	NM 145316	9	72298	23366
A9	0000	l	9	723326	727278
A9	060063	dJ744124.2-001	•	727240	34760
A9	ENSESTT00000035547		9	37272498	37294209
A 9	0229492	C6orf197	9	37298967	37347600
A 9	00000		9	33132	34760
A 9	0000035		9	37331816	733928
A9	96909000	RNF8-001	9	736	37409364
A 9	000003555		9	37368716	38620
A9	0229866	RNF8	9	79	37395990
A9	00003		9	738350	0587
A9	90090	RNF8-002	9	738352	39164
A9	0000355		9	37383557	40586
A9	000003555		9	73835	740587
A9	000003555	٠	9	738355	74058
A9	000003555		9	39155	740587
A9	00000		9	37447848	747423
A 9	00060063	dJ153P14.1-009	9	37447850	745871
A 9	000003555		9	37447850	747423
A 9	000600637	dJ153P14.1-002	. 9	74478	747669
64	9009000	53	9	37447851	37496137
6 A	0259729	15	9	37450261	37.496137
0 N	009000	dJ153P14.1-008	9	37467109	37473320
A9	000003555		9	37474283	37488203

Ę	8 L C 3 O O O O O DIVILITIMO	J.T153P14 1-003 6	37474290	37476703
A C	000003555	000 1.5110010	7474290	7476703
7 A	9000	3P14.	47750	74959
9 A	000600637	J153P14.1-004	748819	382
A 9	000003556		37489154	
94	0000035	9	748915	749387
9 A	000600638	dJ153P14.1-007 6	74899	749745
A9	000003556		8995	74974
A9	000600638	P14.1-006	74	749577
0 A	000000039	53P14.2-001	37497551	37514553
6 A	000003		749756	751452
94	0259975	Q9P0B6 6	749756	751455
0 A	0000	9	756	9949
0 N	000003557	9	749771	751454
6 A	000600639	P14.2-002	37497716	751455
0 d	000000037	4.3-001	55	756138
0 4	000003557		755818	756139
0 A	0000000637	dJ153P14.4-001 6	756118	756234
0 A	000003556		756463	756
0 4	000600637	dJ153P14.5-001 6	463	37565491
014	000003557		765173	766087
0 A	000600640	dJ402N21.2-001 6	9/	6917
9 A	0297153	MDGA1 6	199	771144
6 A	02298	Q8NBE3 6	37652690	766085
0 4	00000		37653259	9/
0 4	0000003556	9	6381	9/
6 A	0000003557	9	66450	169991
0 4	0000003556	9	766450	166908
6 A	000000033	dJ402N21.1-001 6	767039	771157
A9	000000355	9	37672943	37711576

A9	OTTHUMT00006006402	dJ441A12.1-001 6	783	78338
A9	ENSESTT00000035566	9	37833212	783397
A9	00000355	9	37834162	4463
A9	00060064	TEX27-001 6	37834162	38169252
A9	ENSESTT00000035565	9	78	38166902
A9	02872	TEX27 6	783457	38167020
A9	OTTHUMT00006006407	-002	37944570	38097088
A9	ENSESTT00000028267	9	80	801855
A9	OTTHUMT00006006404	.1-001	801746	801794
A9	0	TEX27-003 6	∞	38077291
A9	0		807635	816841
A9	\circ	-004	813120	81569
A9	000600641	5F6.2-001	817743	817843
A9		22I12.1-004	38185948	865444
A9	000600641	112.2-001	38188304	38191924
A9	0		18958	835972
A9	\circ		818968	827107
A9	032090	Q8NAH5 6	819399	819449
A9	009000	[12.1-002	830291	859490
A 9		9	38496227	
A9	000600641	bA430C17.1-001 6	9632	849716
A9	OTTHUMT00006006422	2.1 - 001	38592231	9019
A9	100060064	dJ319M7.2-001 6	60195	0316
7 A	032	BIBD9 6	38607118	38612725
A 9	009000	I12.1-003		98
6 K	000		38690574	9784
A 9	0000600643	GLO1-001 6	869057	87177
79	0024474	GL01 6	069	871777
A 9	0000002	9	9057	871178
A9	000000282	9	38691212	38699147

38717784	38717784	869	38717784	38717784	38717784	38729848		38749145	38986711	39045150	904515	904542	877932	38878623	38885121	888817	894600	38967730	894804	38944241	894278	38947548	38947548	38967720		39027120	39045160	90546	39102374
38691212	38691212	38691365	38696639	38696641	38697434	38728682	7286	38729972	38737477	873747	873775	874914	877753	38872332	38878600	38887623	38937660	93766	9336	94072	38942662	38943981	38943981	38958559	38966101	38998885	90	39054234	39063429
10																													
w	9	9	9	9	9	9	© .	9	9	9	9	9		9	9	9	9	9	9	9	9		9	9	9	9	છ	1 6	9
						dJ503A6.2-001		OSINES	DNAH8-003	DNAH8-002	DNAH8-001	DNAH8	dJ217P22.2-001		DNAH8-004		dJ207H1.3-001	dJ207H1.3-002			dJ207H1.2-001	dJ207H1.3-003					i	dJ202I21.3-00	GLP1R-001
00000028258	0	0000028	0000028259	0000028260	0000028261	0006006432	0000028257	0327475	00601	00006012037	00006012036	0244699	00006011850	00002		00002825	0			0000028251	00006011974	00006006440	0000028256	0	0	00000282	0	9009000	00006006444
ENSESTT		0	ENSESTT0	ENSESTT00	ENSESTT00	OTTHUMT00	ENSESTT00	ENST00000	OTTHUMTOO	OTTHUMT00	OTTHUMT00	ENST00000	OTTHUMT00	ENSESTT00	OTTHUMTO	ENSESTT00	OTTHUMTO	OTTHUMT00	ENSESTT00	ENSESTT0	OTTHUMT0	OTHUMIO	ENSESTIO	ENSESTT0	ENSESTT0	ENSESTIO	ENSESTIO	OTHUMT0	OTTHUMT0
A9	A9	A9 .	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	À9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9

~	4	\sim	203	320	720	583	702	702	081	4		759	053	137	209		171	599	\vdash	 1	36	30	790	716	803	946	037	. 605
910	9124	9129	9124	391298	9129	9127	9129	129	9244	9243	9243	9243	9329	9315	9319	9328	337	933	9337	933	935	39400	39445	39554	39368	39445	39740	39599
	911869	911869	39118695	39118695	39119524	39124952	91	39127885	39203604	320552	39205943	320877	39313632	93140	31405	931405	9329	9329	93	9332	93507	39350785	39358338	39358338	39368378	39434570	39554634	39554831
9	9	O	01 6	_	9	001 6	-002 6	9	9	9	9	9	9	9	ဖ	9	ဖ	9	9	9	9)1 6		9	Н		-001 6	v
GLP1R			dJ202I21.1-001	dJ202121.1-003	C6orf64	21.5-	121.1		KCNK5-001	KCNK5			KCNK17-001			KCNK17	KCNK16-001		KCNK16	-		dJ137F1.4-001	C6orf102	086T87	dJ137F1.3-00	dJ188D3.1-001	3.1	
0	298	296	446	-		454	4		45		1294	3295		9	9	6	5462	8290		3291		6460	ı	» «	6458	9	47	α
ENST0000022990	0000028	ENSESTT000000282	OTTHUMT00006006	0	\circ	009000	009000	0	009000	029716	ENSESTT00000028	ENSESTT0000002829	OTTHUMT00006006	ENSESTT000000282	ENSESTT00000028		000		021119			OTTHUMT00006006		, _	009000		OTTHINE 000000000000000000000000000000000000	
A9	A9	A9	A9	A 9	9 A	6 K	6 K	6 K	9 A	9 A	5 A	2 A	0 A	A9	A 9	9 A	A9	9 A	9 A	6 A	A9	D A	0	0 6	0 0	00	0 6	

395929 973994 959290 960097 956957	59958 61089 68911 72959	73992 187970 191950	387580 387580 387610 388215	9919499 991949 989309 989340	39911984 39912011 39912011 39913571 39919761	39914702 39919496 39918030 39926973
955910 55916 55917 55917 55917		70626 180700 180764 183673	86340 87087 87087	987087 988235 988496 988797 990203	39903421 39903505 39903505 39911507 39911802	39911971 39917315 39917519 39919690
dJ1043E3.1-003 6 6 dJ1043E3.2-001 6	. 6 dJ1043E3.1-002 6 dJ1043E3.1-004 6		.1-006	1.1-001 1.1-003 1.1-004 1.1-005	w w	bA61113.2-001 6 6 MOCS1-005 6
OTTHUMT00006006472 ENST00000287152 ENSESTT00000028288 ENSESTT00000028285 OTTHUMT00006006468	ENSESTT00000028287 OTTHUMT00006006471 ENSESTT0000028283	00002828 00002826 274867	0002827 0002827 0600648 0600648		00600648 00600648 000002828	000600647 000002827 000002828 0000005828
A9 A9 A9 A9	A A 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9	A A A A A A A A A A A A A A A A A A A	A A A A A A A A A A A A A A A A A A A	A99 A99 A99	0 A A A A A A A A A A A A A A A A A A A	A99 A99 A99 A99 A99

	992760	994199	94231	994909	994910	992691	94901	994217	992802	994910	994702	994905	997342	39973427	01482	01486		39447	40394479	36062	36074	38406	40394479	39447	39449	3944	60205	019	40601916
39919690	919	39919690	9919	39919690	39919690	99	992015	39920988	992136	99244	992686	39941918	997300	7300	000740	40014193	028616	40349548	505	5893	40358938	40373338	40392931	39		393	4061	40406228	40447652
9	9	9	9	9	9	9	9	9	9	9	9	و	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
MOCS1-006	00-	0	MOCS1-001	00-	MOCS1-008		MOCS1	MOCS1			MOCS1-004			11.	ഥ		bA552E20.1-001	bA535K1.1-003	bA535K1.1-004		52E	DA552E20.4-001	bA535K1.1-001	-00			DA535K1.2-001	Q9ULH4	
OTTHUMT00006006505	006006506	0060065	OTTHUMT00006006500	OTTHUMT00006006501	00000000	ENSESTT00000028275	œ	~	ENSESTT00000028278	ENSESTT00000028276	OTTHUMT00006006503	002	ENST00000320371	00600649	000	33	900	00	OTTHUMT00006006525	ENSESTT00000026515	OTTHUMT00006006518	OTTHUMT00006006520	OTTHUMT00006006522	000600652	000002651	0	OTTHUMT00006006532	0	ENSESTT00000026512
9 A	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	. 6A	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9	A9

230	74	907		515	344	72		716		61654	9	29	19	91981	7.1	48	7.1	53	17	591	11108	15	715	45394	1006	1006		14808
728	28	31	7309	7309	34	46	48	48	48	∞	52	49	51	51	52	52	\sim	53		53	53			753	753	753	753	753
72820171	286711	308871	73089280	309267	73461485	65597	74836231	18392	185376	₹ť!	192836	492843	516265	516265	519560	520311	520316	525474	52555	525936	75270434	S	75270434	75270434	30685	75307549	31064	75314345
18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18
		GALR1						SALL3			ATP9B							NEATC1		NM 172387	I							
000000568	ENSESTT000000056802 ENST00000309607	29972	ESTT0000005	0005250	000525	0005247	00000	00000299466	0005	0005247	107671	0000	000006596	STT0000006596	STT0000006596	355000000TIS	ESTT0000005597	13506	9.0000	329101	00000	00006597	76590000	70000000	75550000011555 555500000011555	10000000000000000000000000000000000000	000000	34423
A10	A10	A10	A10	A10	A10	A10	A10	A10	A10	A10	A10	A10	A10	A10	A10	210 210	010 010	710	A10	010 010	710	016	A10	A10		ALU		AIO A10

310501 55098 38729 38830 40450 41586	553859 561348 559549	56262 57393 51348 61348	575879 576227 576251 581000	58098. 58098. 58098. 58098. 58098. 58098.	75802836 75809836 75775293 75826139 75831889
	550096 553877 553892	56169 56383 57394 58801 59453	572264 576144 576144 576146	576256 576256 576256 576256 576265 576265	75763093 75774508 75823637 75825557
18 18 18 18 18	188 188	18 18 18 18	18 18 18 .	18 18 18 18 18 18	18 18 18 18
	NM_182570 CTDP1 NM_048368	ı	KCNG2 NM_025078	l	Оденеро
ENSTOO0003340: ENSTO000033392 ENSESTTO00006 ENSESTTO00006 ENSESTTO00006	ENST0000031700 ENST0000029954 ENST0000007543		ENST0000316249 ENSESTT000006600 ENSESTT000006600 ENST00000316111	ENSESTT0000006 ENSESTT0000006 ENSESTT0000006 ENSESTT0000006 ENSESTT0000006	A10 ENST00000262199 A10 ENSESTT00000066003 A10 ENSESTT00000065984 A10 ENSESTT00000065998

831846 758475 32383 7583689 32383 7584755 32384 7584745 32396 7584733	32490 7584739 32541 7583576 32715 7584751	93335 759053 93389 759011 93389 759053	93434 7590535 93473 7590491	96424 7590537 26233 7593811	66162 7599720 89961 7599286	04909 7600613 16631 7610420 16997 7610440	39710 7605963 96497 1324035	324035 429755	194247 14194570 607036 14683474	10088 1471267	727207 14900993 727207 14900993	27207 1490099
75 75 75 75 75 75 75 75 75 75 75 75 75 7	.8 758 .8 758 .8 758	5 2 5	75	3 75	3 75 3 75	3 76	76 76 13	13	14 14	14	14 14	14
DIMI_HUMAN 1	н н	NM_024805	Q8WZ65		NM_014913	ARD6G	MPDZ		NM 178566	,	NM_144966 NM_144966	144966
			O ¹		Ż	Ω ,	M	E Z	Z	0	Z Z	i Z
ENST00000269601 ENSESTT00000065991 ENSESTT00000065993 ENSESTT00000065993	ENSESTT00000065994 ENSESTT00000065997 ENSESTT00000065992	306735 30006598 30006598	00006599 262197	ENSESTT00000065987 ENSESTT00000065988	262198. 00006598	ENSESTT00000052575 ENST00000314741 ENSESTT0000052576	00005257 319217.1	319198.	331870.	276911.	ENST00000297595.3	297593.
_		A10 A10 A10										

A11	ENST00000297615.2	NM_152574	O	15161561	15161561 15297250
A11	ENST00000336042.1	NM 152574	6	15161561	15297250
A11	ENST00000297627.1	SNAPC3	0	15412732	15455830
A11	ENST00000336277.1	SNAPC3	0	15412732	15455830
A11	ENST00000297635.1	PSIP2	6	15454067	15500982
A11	ENST00000285482.4		6	15542895	15613411
A11	ENST00000297641.1	NM 173550	ത	15734586	15961895
A11	ENST00000318677.2	NM_173550	თ	15734586	15961895
A11	ENST00000309604.2	NM 017637	9	16408579	16427061
A11	ENST00000317612.2	NM_017637	6	16408579	16427061
A11	ENST00000316584.1	NM_152576	თ	16517183	16517287
A11	ENST00000297642.1	NM_017738	ത	17125064	17485003
A11	ENST00000262360.2	NM_017738	თ	17125064	17485003

WHAT IS CLAIMED IS:

5

10

20

25

30

1. A method for identifying an antineoplastic agent, comprising:

- (a) contacting a test compound with a cell that expresses one or more amplicons of Table 2 having an amplification ratio of at least 2.0; and
- (b) determining a change in said amplification ratio due to said contacting;

wherein a change in said amplification ratio due to said contacting indicates that said test compound has gene modulating activity

thereby identifying said test compound as a gene modulating agent.

- 2. The method of claim 1 wherein said change in expression is a decrease in expression.
- 15 3. The method of claim 2 wherein said decrease in expression is a decrease in copy number of the gene.
 - 4. The method of claim 1 wherein said cell was genetically engineered to express said amplicon.

5. A method for identifying an antineoplastic agent, comprising:

- (a) contacting a test compound with a cell that expresses at least one gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 3049 and under conditions promoting expression of said gene; and
- (b) determining a change in expression of said gene as a result of said contacting

wherein a change in expression indicates gene modulation thereby identifying said test compound as a gene modulating agent.

6. The method of claim 5 wherein said change in expression is a decrease in expression.

7. The method of claim 5 wherein said decrease in expression is a decrease in copy number of the gene.

- 8. The method of claim 5 wherein said gene comprises a nucleotide sequence of one of SEQ ID NO: 1 3049.
 - 9. The method of claim 5 wherein said cell was genetically engineered to express said gene.
- 10. A method for detecting the cancerous status of a cell, comprising detecting elevated expression in said cell of at least one gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 3049 whereby such elevated expression is indicative of cancerous status of the cell.

15

- 11. The method of claim 10 wherein said elevated expression is an elevated copy number of the gene.
- 12. A method for identifying a compound as an anti-neoplastic agent, 20 comprising:
 - (a) contacting a test compound with a polypeptide encoded by a gene selected from SEQ ID NO: 1-3049,
 - (b) determining a change in a biological activity of said polypeptide due to said contacting,
- wherein a change in activity indicates anti-neoplastic activity and thereby identifies such test compound as an agent having antineoplastic activity.
- 13. The method of claim 12 wherein said change in biological activity is30 a decrease in biological activity.

14. The method of claim 12 wherein said biological activity is an enzyme activity.

15. The method of claim 14 wherein said enzyme is selected from kinase, protease, peptidase, phosphodiesterase, phosphatase, dehydrogenase, reductase, carboxylase. transferase, deacetylase and polymerase.

5

15

30

- 16. The method of claim 15 wherein said kinase is a protein kinase.
- 10 17. The method of claim 15 wherein said kinase is a serine or threonine kinase.
 - 18. The method of claim 15 wherein said kinase is a receptor tyrosine protein kinase.
 - 19. The method of claim 15 wherein said protease is a serine protease, cysteine protease or aspartic acid protease.
- 20. The method of claim 15 wherein said transferase is a 20 methyltransferase.
 - 21. The method of claim 20 wherein said methyl transferase is a cytidine methyltransferase or an adenine methyltransferase.
- 25 22. The method of claim 15 wherein said deacetylase is a histone deacetylase.
 - 23. The method of claim 11 wherein said carboxylase is a γ -carboxylase.
 - 24. The method of claim 15 wherein said peptidase is a zinc peptidase.

25. The method of claim 15 wherein said polymerase is a DNA polymerase.

- 26. The method of claim 15 wherein said polymerase is a RNA 5 polymerase.
 - 27. The method of claim 12 wherein said biological activity is a membrane transport activity.
- 10 28. The method of claim 12 wherein said polypeptide is a cation channel protein, an anion channel protein, a gated-ion channel protein or an ABC transporter protein.
 - 29. The method of claim 12 wherein said polypeptide is an integrin.

15

- 30. The method of claim 12 wherein said polypeptide is a Cytochrome P450 enzyme.
- 31. The method of claim 12 wherein said polypeptide is a nuclear 20 hormone receptor.
 - 32. The method of claim 12 wherein said biological activity is a receptor activity.
- 25 33. The method of claim 12 wherein said receptor is a G-protein-coupled receptor.
 - 34. The method of claim 12 wherein said polypeptide is contained in a cell.

30

35. A method for identifying an anti-neoplastic agent comprising contacting a cancerous cell with a compound found to have anti-neoplastic

activity in the method of claim 12 under conditions promoting the growth of said cell and detecting a change in the activity of said cancerous cell.

36. The method of claim 35 wherein said change in activity is a decrease in the rate of replication of said cancerous cell.

5

37. The method of claim 35 wherein said change in activity is a decrease in the total number of progeny cells that can be produced by said cancerous cell.

10

- 38. The method of claim 35 wherein said change in activity is a decrease in the number of times said cancerous cell can replicate.
- 39. The method of claim 35 wherein said change in activity is the death of said cancerous cell.

15

40. A method for treating cancer comprising contacting a cancerous cell with an agent first identified as having gene modulating activity using the method of claim 1, 5, or 12 and in an amount effective to cause a reduction in cancerous activity of said cell.

20

41. The method of claim 40 wherein said cancerous cell is contacted *in vivo*.

25

- 42. The method of claim 40 wherein said reduction in cancerous activity is a decrease in the rate of proliferation of said cancerous cell.
- 43. The method of claim 40 wherein said reduction in cancerous activity is the death of said cancerous cell.
- 30 44. The method of claim 40 wherein said cancer is a cancer of breast, colon, lung or prostate tissues.

45. A method for treating cancer comprising contacting a cancerous cell with an agent having affinity for an expression product of a gene corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1-3049 and in an amount effective to cause a reduction in cancerous activity of said cell.

- 46. The method of claim 45 wherein said expression product is a polypeptide.
- 10 47. The method of claim 45 wherein said agent is an antibody.
 - 48. A method for monitoring the progress of cancer therapy in a patient comprising monitoring in a patient undergoing cancer therapy the expression of a gene corresponding to a polypeptide having a sequence selected from SEQ ID NO: 1 3049.
 - 49. The method of claim 48 wherein said gene comprises a sequence of SEQ ID NO: 1 3049.
- 50. The method of claim 48 wherein said cancer therapy is chemotherapy.
 - 51. The method of claim 48 wherein said cancer is a cancer of breast, colon, lung or prostate tissues.

25

30

15

5

52. A method for determining the likelihood of success of cancer therapy in a patient, comprising monitoring in a patient undergoing cancer therapy the expression of a gene corresponding to a polynucleotide having a sequence of one of SEQ ID NO: 1 – 3049 wherein a decrease in said expression prior to completion of said cancer therapy is indicative of a likelihood of success of said cancer therapy.

53. The method of claim 52 wherein said gene comprises a sequence of SEQ ID NO: 1-3049.

- 54. The method of claim 52 wherein said cancer therapy is 5 chemotherapy.
 - 55. The method of claim 52 wherein said cancer is a cancer of breast, colon, lung or prostate tissues.
- 10 56. A method for producing test data with respect to the anti-neoplastic activity of a compound comprising:
 - (a) identifying a test compound as having anti-neoplastic activity using a method of claim 12;
- (b) producing test data with respect to the anti-neoplastic activity of said test compound sufficient to identify the chemical structure of said test compound.
 - 57. A method for determining the progress of a treatment for cancer in a patient afflicted therewith, following commencement of a cancer treatment on said patient, comprising:

20

- (a) determining in said patient a change in expression of one or more genes corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 3049; and
- (b) determining a change in expression of said gene compared to
 expression of said one or more determined genes prior to commencement of said cancer treatment;

wherein said change in expression indicates progress of said treatment thereby determining the progress of said treatment.

30 58. The method of claim 57 wherein said change in expression is a decrease in expression and said decrease indicates success of said treatment.

59. A method for determining the progress of a treatment for cancer in a patient afflicted therewith, following commencement of a cancer treatment on said patient, comprising:

(a) determining in said patient a change in expression of one or more genes corresponding to a polynucleotide comprising a nucleotide sequence of SEQ ID NO: 1 – 3049; and

5

10

(b) determining a change in expression of said gene compared to expression of said one or more determined genes prior to commencement of said cancer treatment;

wherein said change in expression indicates progress of said treatment thereby determining the progress of said treatment.

60. The method of claim 59 wherein said change in expression is a decrease in expression and said decrease indicates success of said treatment.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/07748

		101/08037077	
A CT AS	SIFICATION OF SUBJECT MATTER		
A. CLAS: IPC(8)	: C12Q 1/68; C07H 21/04		
T 70 OT	. 425/6, 526/22 1 23 5	1 Junification and IPC	
According to 1	International Patent Classification (IPC) or to both nati	onal classification and it C	
U, 122	OS SEARCHED		
Minimum doo	cumentation searched (classification system followed b	y classification symbols)	
U.S. : 43	5/6; 536/23.1, 23.5		
Documentation	on searched other than minimum documentation to the	extent that such documents are include	ed in the fields searched
	ta base consulted during the international search (name	of data base and, where practicable,	search terms used)
Electronic dat	ta base consulted during the international search (name ontinuation Sheet	of data base arts, was a	
Please See Co	ontinuation Sheet		
	THE PROPERTY AND		
	JMENTS CONSIDERED TO BE RELEVANT	propriete of the relevant passages	Relevant to claim No.
Category *	Citation of document, with indication, where ap	00%) especially sol 6 25 and Table	
x	US 5,776,683 A (SMITH et al) 07 July 1998 (07.07.1	1998), especially col. 0, 25 and 10010	
	SQUIRE et al. High-resolution mapping of amplification	ions and deletions in pediatric	1-4
Y	osteosarcoma by use of CGH analysis of cDNA micro	arrays. Genes, Chromosomes &	
	Cancer. 2003, Vol. 38, pages 215-225, especially page	e 216 and Table 1.	
	Cancer. 2005, vol. 50, pages 210 220, e-p-stray, re		1
			į
		G	
Further	r documents are listed in the continuation of Box C.	See patent family annex.	La etianal filing date or priority date
* 5	Special categories of cited documents:	and not in conflict with the applica	international filing date or priority date tion but cited to understand the
MAD J	t defining the general state of the art which is not considered to be of	principle or theory underlying the	invention
"A" document particular	r relevance	"X" document of particular relevance;	the claimed invention cannot be
• •	plication or patent published on or after the international filing date	considered novel or cannot be con-	sidered to involve an inventive step
		when the document is taken alone	
"L" documen	it which may throw doubts on priority claim(s) or which is cited to the publication date of another citation or other special reason (as	"Y" document of particular relevance;	the claimed invention cannot be step when the document is combined
establish specified	(1)	considered to involve an inventive with one or more other such clocur	nents, such combination being obvious
"O" documen	at referring to an oral disclosure, use, exhibition or other means	to a person skilled in the art	
		"&" document member of the sarxie pa	tent family
"P" documen	nt published prior to the international filing date but later than the date claimed	2552	
• •		Date of mailing of the international	search report
Date of the	actual completion of the international search	Date of mailing of the international 2 I FEB: 2	nas
18 January 2	2006 (18.01.2006)	~ 4	_
Name and m	nailing address of the ISA/US	Anthorized office	sixce for
M	nil Stop PCT, Attn: ISA/US	Carla Myers	www.for
Co	mmissioner for Patents	1	-
P.C	O. Box 1450 exandria, Virginia 22313-1450	Telephone No. 571-272-1600	
Facsimile N	Jo. (571) 273-3201		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/07748

Box No. II	Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)
This internat	ional search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1.	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2.	Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box No. III	Observations where unity of invention is lacking (Continuation of item 3 of first sheet)
	ional Searching Authority found multiple inventions in this international application, as follows: ontinuation Sheet
1.	As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.	No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-4, with respect to the amplicon comprising chromosome 8q24.13
Remark on 1	Protest The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
	The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

Form PCT/ISA/210 (continuation of first sheet(2)) (April 2005)

International application No. PCT/US05/07748

INTERNATIONAL SEARCH REPORT

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional examination fees must be paid.

Groups 1-47, claims 1-4 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing one of the 47 amplicons set forth in Table 2. For example, Group 1 is drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing the 5.3 MB amplicon comprising chromosome 8q24.13. Upon election of one of the groups, please specify the amplicon to be searched.

Groups 48-3097, claims 5-9 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing one of the sequences of SEQ ID NO: 1-3049 and assaying for a change in the level of expression of one of the sequences. For example, Group 48 is drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell

containing SEQ ID NO: 1. Upon election of one of the groups, please specify the SEQ ID NO of the elected

group to be searched.

Groups 3098-6147, claims 10-11 (in part), drawn to methods for identifying a cancerous state of a cell by assaying for the sequence of one of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

Groups 6148-9196, claims 12-34 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049 and assaying for a change in the activity of the polypeptide. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched. Further, it is noted that claim 23 has been included with this grouping because it appears that claim 23 intends to depend from claim 15, rather than claim 11.

Groups 9197-12,245, claims 35-39 (in part), drawn to methods for identifying an antineoplastic agent by contacting a test compound with a cell containing one of the sequences of SEQ ID NO: 1-3049 and assaying for a change in the cancer cell growth of said cell. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

Groups 12,246-15,294, claims 40-47 (in part), drawn to methods for treating cancer by using a compound that effects the activity of a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the corresponding SEQ ID NO of the elected group to be searched.

International application No. PCT/US05/07748

INTERNATIONAL SEARCH REPORT

Groups 15295-18343, claims 48-55 and 57-60 (in part), drawn to methods for monitoring the progress of a cancer therapy by assaying for the level of a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

Groups 18,344-21,392, claim 56 (in part), drawn to methods for producing data comprising producing test data sufficient to identify the chemical nature of a test compound that effects the activity of a polypeptide encoded by one of the sequences of SEQ ID NO: 1-3049. Upon election of one of the groups, please specify the SEQ ID NO of the elected group to be searched.

The inventions listed as Groups 1-21,392 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

In accordance with 37 CFR 1.475(d) Applicant is entitled to an examination of the first product, method of making said product and method of using said product. In the instant case, the first method is one which requires one of the 47 amplicons of Table 2. This product is not required for the methods set forth in the remaining groups. Thereby, Groups 48-21,392 constitute distinct groups which do not share the same corresponding technical feature of groups 1-47. Further, unity of invention exists only when there is a technical relationship among those inventions involving one or more of the same or corresponding technical features. The expression 'special technical feature" means those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. The technical feature linking the claims 5-60 is the HAS2 gene. However, the HAS2 gene was known in the art at the time the invention was and thereby does not constitute a contribution over the prior art (see NCBI Database, GenBank Accession No. U54804). Accordingly, there is no special technical feature linking the recited groups, as would be necessary to fulfill the requirement for unity of invention.

It is also noted that each of the present claims has been presented in improper Markush format, as distinct methods are improperly joined in the claims. Each amplicon of Table 2 and each nucleic acid sequence of SEQ ID NO: 1-3049 is structurally and functionally distinct from and has a different special technical feature than each other the amplicons and nucleic acid sequences. The chemical structure of each amplicon and nucleic acid sequence differ

from each other. For example, a polynucleotide comprising SEQ ID NO: 1 is chemically, structurally, and functionally different from a molecule comprising SEQ ID NO: 2. Given the differences in the structure, function and effect the amplicons of Table 2 and the sequences of SEQ ID NO: 1-3049, these compounds are not considered to share a special technical feature as would be necessary to fulfill the requirement for unity of invention. These distinct compounds do not have both a "common property or activity" and a common structure as would be required to show that the inventions are "of a similar nature." As the products and methods encompassed by the claims do not share a special technical feature, the distinct products and methods may not properly be presented in the alternative. Accordingly, the claims have been separated into a number of groups corresponding to the number of different inventions encompassed by the claims, and the claims will be searched only as they read upon the invention of the elected group

Additionally, each of the claimed methods have different objectives and require different process steps. The methods of claims 1-4 require cells containing one of the amplicons of Table 2 and requires assaying for a change in the amplification ratio of the amplicon. The methods of claims 5-9 require the use cells that contain one of the sequences of SEQ ID NO: 1-3049, and requires assaying for a change in gene expression by assaying for mRNA or protein levels in order to

accomplish the objective of identifying a antineoplastic agent. The methods of claims 10-11 require assaying for the level of one of the sequences of SEQ ID NO: 1-3049 in order to accomplish the objective of identifying a cancerous state of a cell. The methods of claims 12-34

require contacting a cell with a test agent and assaying for a change in biological activity of a polypeptide encoded by SEQ ID NO: 1-3049. The methods of claims 35-39 require contacting a cell with a test compound and assaying for the cancerous state of a cell. The methods of

claims 40-47 require administering an agent to an individual in order to accomplish the objective of treating cancer. The methods of claims 48-55 and 57-60 require determining gene expression levels of a polypeptide of one of SEQ ID NO: 1-3049 and assaying for polypeptide levels in order to accomplish the objective of monitoring the progress of cancer therapy. The method of claim 56 requires identifying test compounds that have

Form PCT/ISA/210 (extra sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No. PCT/US05/07748

antineo plastic activity and producing test data in order to obtain sufficient data to identify the chemical structure of the test compound. In addition to differences in objectives, effects, and method steps, it is again noted that the claims of the present Groups are not directed to the detection or identification of molecules having the same or common special technical feature, for the reasons discussed above.
Continuation of B. FIELDS SEARCHED Item 3: WEST: USPT, JPAB, EPAB, DWPI, PGPUB; DIALOG: MEDLINE, CA, BIOSIS, EMBASE search terms: 8q24.13, 8q24.1; amplification or amplified or copy number; cancer or tumor or neoplasm
-